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THE EFFECT OF GLUTAMIC ACID ON THE HYDROGEN ION CONCENTRATION (pH) OF THE URINE IN PETIT MAL TYPES OF EPILEPSY

A Daily Record for One Year of the Urinary pH of an Epileptic Patient with an Allergic Background, to Whom Four Forms of Glutamic Acid Were Administered in Various Daily Amounts

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A MODIFICATION in the severity and frequency of petit mal types of epilepsy has been found possible through increasing the hydrogen ion concentration of the urine to a pH of 5, 4 or lower by the daily administration of glutamic acid in various forms and amounts.

This biochemical metabolic modification (soil alteration) has been reported of benefit in allergic patients recently by Forman[5] who states he "has been accustomed for a number of years to use glutamic acid hydrochloride in 5-grain capsules, after meals, because of low gastric acidity in allergic individuals."

Bookhammer[1] in a recent lecture at a seminar on Mental Hygiene, under the auspices of the Philadelphia County Medical Society, stated that he had obtained improvement in patients with epileptic seizures by the use of a teaspoonful of glutamic acid added to a glass of milk, taken three times daily after meals. He reported, however, considerable difficulty in securing the material.

In August, 1943, Price, Waelsch and Putnam[10] were the first to report "On the Use of dl-Glutamic Acid Hydrochloride in Treatment of Petit Mal and Psychomotor Seizures." They stated that grand mal seizures were unaffected by the administration of the glutamic acid. The encouraging results, reported by the addition to known anticonvulsive therapy, of glutamic acid is recorded by them in a summarized detail of eight patients, in all of whom the minor seizures were benefited.

In reporting[12,13] two series of epileptic patients, totaling 305 cases, I found some form of allergy present in over fifty per cent, and in the an-

cestors of these 305 patients there occurred 517 instances of allergy in one form or another (asthma, hay fever, urticaria, eczema, migraine) or a demonstrable gastrointestinal disturbance of probable allergic origin.

As a metabolic alterative, I have used for over thirty-five years, the intramuscular injection of a solution of venom protein (crotalin) in most of the more than 1,000 epileptic patients I have studied and treated since 1909.[14] The mechanism of the action of crotalin has been shown to include its eosinophilogenic properties[15], its plasma activating influence[17], its ability to increase cell permeability[4,7,11,16], its action in causing peripheral vascular dilatation[4], its altering influence on enzymes[9] and colloids[6] together with other modifications of metabolism.

PRESENT CLINICAL INVESTIGATION

During the past eighteen months, in the treatment of six patients who were subject to both grand and petit mal types of epileptic seizures, I have added one or another form of glutamic acid to their other medications. These patients were selected because all previous therapy had had little or no effect on their petit mal seizures. All six patients had been receiving dilantin sodium either alone or in combination with phenobarbital before coming under my care, and the intervals of their convulsive seizures had been variously lessened in frequency or modified in severity, but the petit mal manifestations were little or not at all affected.

The anticonvulsive sedative therapy was continued while I treated these patients, and, in addition, they were given, every seven to fourteen days, an intramuscular injection of crotalin, the strength dose of which was guided by the percentage of eosinophils[15] in the differential blood counts made just before and twenty-four hours after an injection. The dose of crotalin ranged from 1/400 to 1/50 of a grain.

Glutamic acid was then added to the crotalin-dilantin-phenobarbital therapy, with a noticeable reduction in frequency, and modification in the character and severity of the petit mal seizures. The effect, to a greater or less degree, was practically the same in all six patients. Accordingly, the data from one patient only is reported in detail as an illustration. All six patients used a diet with a preponderance of protein, i.e., food with acid ash, in the proportion of two to three parts to one part alkaline ash base, as originally suggested by MacQuarrie.[8] No special article or type of food was excluded, unless there was a natural antipathy of the patient to a given food or a definite allergic response was shown to certain foods by skin testing.

FORMS OF GLUTAMIC ACID USED

Three forms of Glutamic Acid (Lederle) were used, i.e., *dl*-Glutamic Acid Hydrochloride in 0.5 gm. *capsules; d*-Glutamic Acid Hydrochloride in 0.58 gm. *capsules,* and Glutamic Acid Hydrochloride in 0.324 *capsules* (the latter stocked as "Glutan," H-C-L). All were furnished through the courtesy of Benjamin W. Carey, M.D., Director of Lederle Labora-

tories. Natural dextrorotatory Glutamic Acid (Parke, Davis & Co.) in 0.5 gm. *tablets* were also used at times in clinical comparison. The latter form of Glutamic Acid, i.e., the natural dextrorotatory, has been designated in a second paper by Waelsch and Price[17], with a nomenclature of *l* (+) Glutamic Acid, which they report of as much clinical value as the *dl*-Glutamic Acid Hydrochloride.

CASE HISTORY AND MEDICATION

The data of the clinical investigation reviewed in detail in this case includes: the patient's and her families' history; the anticonvulsant and metabolic alterative medication used; the various size doses and forms of Glutamic Acid administered, together with the daily record, for one year, of the patient's urinary pH.

The patient, at the age of thirty-three years, has been married for seven years. She is a college graduate, has done some high school teaching and her own housework since marriage.

She was a first-born, full-term baby, instrumentally delivered, breast-fed for a few months but owing to "bilious attacks" did not gain so the diet was changed to condensed milk, and thereafter there were fewer and modified gastrointestinal upsets. No specific food sensitivity could be determined. No spasms occurred in infancy, she had measles at third year, chicken pox at fifth year and whooping cough after starting school. She was subject to "strawberry rash" as a child, and after adolescence, to ivy poisoning. Milk and cream have always, since childhood, caused "gastrointestinal upsets." There is also an antipathy to butter. Skin tests, however, were negative to milk, egg and wheat. Menstruation was established at thirteenth year, has always been of 28-day type, and without cramps. No accidents or injuries have ever occurred causing unconsciousness.

Seizure History.—Petit mal started at seventh year and continued at irregular intervals of a few days to a week with an occasional longer interval. The first convulsion occurred at the time the menarche was established in her thirteenth year. The major type of seizure recurred thereafter at intervals of one to three months; petit mal occurring between the convulsive attacks at intervals of from one to three to seven days and occasionally, three, four or five in the same day, but always more likely to occur during or just after a menstrual period. Many of the lighter forms of momentary lapses were referred to by the patient and her family as "haziness." They did not interfere with the patient completing a college course, teaching school for a time and marrying in her twenty-third year. At her twenty-fifth year a three months' pregnancy increased both types of seizures, and was terminated at the third month, but both forms of attacks continued to recur at about the same frequency as they did prior to the pregnancy.

Family Allergic History—The father is subject to neuralgic headaches, ivy poison and urticaria, which has occurred repeatedly following honey sensitivity. Her mother had "uremic" convulsions at the patient's birth, and has been subject to urticaria all her life. Mother's brother, now forty years of age, is subject to convulsive seizures. Maternal grandmother suffered from periodic headaches with vomiting (allergic migraine).

Treatment and Its Effect on Seizures.—Anticonvulsant therapy began with phenobarbital, started after the first grand mal seizure in 1924 and was continued until September, 1940. During the period of report, now available, beginning with Jan-

TABLE I. URINARY pH AND RECORD OF SEIZURES

November 20, 1943–March 13, 1944

Date 1943	1st A.M. or other hour specimen Urinary pH	Total Amount Taken Daily in 3 Doses, after Meals.† Gms.	Record of Seizures and Comment
			dl-Glutamic Acid Hydrochloride (in capsules)
Nov. 20	A.M. 4	3.0	
21	" 7*	4.5	*—30 grs. Sod. Bicarb.—Indigestion.
22	" 5	1.5	
23	" 5	1.5	
24	" 4	1.5	
25	" 6	3.0	
26	" 4	1.5	
27	" 5	1.5	
28	" 4	3.0	
29	" 4	1.5	
30	" 4	1.5	
Dec. 1	" 4	1.5	
2	" 4	1.5	
3	" 5	1.5	
4	" 5	1.5	
5	" 6	4.0	●●—during the day
6	" 4	3.0	●●●—during the day
7	" 4	1.5	
8	" 4	1.5	
9	" 4	1.5	
10	" 4	1.5	
11	" 5	1.5	
12	" 5	1.5	Menstruation—(Dec. 12 to 15)
13	" 5	1.5	
14	" 4	1.5	
15	" 5	1.5	
16	" 4	1.5	
17	" 5	1.5	
18	" 4	1.5	
19	" 6	2.0	
20	" 4	1.5	
21	" 4	1.5	
22	" 4	1.5	
23	" 4	1.5	●— 9 A.M.
24	" 4	1.5	●—10 P.M.
25	" 4	1.5	●— 1 P.M.
26	" 4	3.0	
27	" 4	1.5	
28	" 6	3.0	
29	" 4	1.5	
30	" 4	1.5	
31	10 A.M. 6	4.0	
	3 P.M. 7		●— 6 P.M.
1944			
Jan. 1	A.M. 5	3.0	
2	" 4	1.5	
3	" 4	1.5	
4	" 5	1.5	
5	" 4	1.5	
6	" 5	1.5	
7	" 4	1.5	
8	" 8	3.0	Menstruation—(Jan. 8 to 11)
9	" 4	1.5	
10	" 4	1.5	
11	" 4	1.5	
12	" 4	1.5	
13	" 4	1.5	
14	" 4	1.5	●—6 P.M.
15	" 5	3.0	
16	" 4	1.5	●—2:30 P.M.
17	" 5	1.5	●—9 A.M. and 2 P.M.
18	" 4	1.5	
19	" 6	3.0	
20	" 6	3.0	
21	" 4	1.5	
22	" 4	1.5	
23	" 4	0.5*	●—4:30 A.M. *All day
24	" 4	1.5	
25	" 5	1.5	
26	" 4	1.5	
27	" 4	1.5	
28	4 P.M. 4	3.0	
	6 P.M.		
29	8 A.M. 4	1.5	
	6 P.M. 6		●—6 P.M.
30	A.M. 8	4.0	●—9 A.M.
	" 8		
31	" 4	1.5	
Feb. 1	" 4	1.5	
2	" 6	3.0	

TABLE I. URINARY pH AND RECORD OF SEIZURES (Continued)
November 20, 1943-March 13, 1944

Date 1944	1st A.M. or other hour specimen Urinary pH	Total Amount Taken Daily in 3 Doses, after Meals.† Gms.	Record of Seizures and Comment
Feb. 3	" 4	2.0	
4	" 5	1.5	
5	" 4	1.5	●—6 P.M. Menstruation— (Feb. 5 to 9)
6	" 4	1.5	
7	" 6	3.0	
8	" 4	1.5	
9	" 6	3.0	
10	" 4	1.5	
11	" 4	1.5	
12	" 4	1.5	●—9 A.M.
13	" 6	3.0	
14	" 6	4.0	From Feb. 14 the pH was taken both on arising *and* retiring
	P.M. 4		●—7 P.M.
15	A.M. 6	4.0	
	P.M. 8		
16	A.M. 4	1.5	
17	" 4	5.0	
	P.M. 8		
18	A.M. 4	2.5	
	P.M. 8		●—1:30 P.M.
19	A.M. 4	2.5	
	P.M. 8		
20	A.M. 4	2.5	
	P.M. 6		
21	A.M. 6	4.0	
	7 P.M. 4		°—6:30 P.M.
	11 P.M. 8		
22	A.M. 6	3.0	
23	" 4	1.5	
24	" 8	4.0	
	P.M. 8*		*Soda bicarbonate for indigestion
25	A.M. 8	3.0	
26	" 8	1.5	
27	" 4	1.5	
28	A.M. 5	3.0	
29	" 6	2.5	
	P.M. 4		°—4:30 P.M.
Mar. 1	A.M. 4	3.0	
	P.M. 4		
2	A.M. 4	1.5	
	P.M. 4		●—6:30 P.M.
3	A.M. 4	1.5	
4	" 4	2.5	●—7 P.M. Menstruation—(Mar. 4 to 7)
	P.M. ..		
5	A.M. 4	2.5	●—7:30 A.M.
	P.M. 8		
6	A.M. 4	1.5	
7	" 4	1.5	
	P.M. 4		
8	A.M. 4	1.5	●—4 P.M.
9	" 4	2.5	
	P.M. 6		
10	A.M. 4	1.5	
11	" 4	2.5	
	P.M. 6		
12	P.M. 4	1.5	°—6 P.M.
13	A.M. 6	3.0	°—3 P.M.

†*dl*-Glutamic Acid
Hcl. Caps. 0.5 Gm. each (Lederle).
Type of Seizures
●—Hazy Attack
°—Petit Mal
x—Grand Mal

Summarized Deductions (Table I): dl-Glutamic Acid Hydrochloride in capsules of 0.5 gm. each were given in three daily doses, totaling in amounts that ranged from 1.5 to 4.5 grammes per day from November 20, 1943, to March 13, 1944.

A urinary pH of 5 or above occurred on 55 days during this period of 114 days, 48% of the days.

Four menstrual periods occurred during these 114 days, and during the days of the four periods the pH of the urine was 5 or above twelve times, 10 per cent of the days during menstruation.

During these twelve times with a pH of 5 or above, six "hazy" manifestations occurred, two of them on the day menstruation began. There were no petit mal or convulsive seizures.

TABLE II. URINARY pH AND RECORD OF SEIZURES
March 14, 1944-April 24, 1944

Date 1944	1st A.M. or other hour specimen Urinary pH	Total Amount taken Daily in 3 doses, after meals.† Gms.	Record of Seizures and Comment
Mar. 14	A.M. 5	4.64	*Note change* in type and dosage of Glutamic Acid (from *dl*-Glutamic Acid to *d*-Glutamic Acid).
	P.M. 8		
15	A.M. 4	4.64	
	P.M. 4		
16	A.M. 4	4.64	
	P.M. 4		
17	A.M. 4	4.64	
	P.M. 8		
18	A.M. 4	4.64	
	P.M. 8		
19	A.M. 6	4.64	
20	A.M. 4	4.64	
	P.M. 4		●—6:30 P.M.
21	A.M. 4	6.96	
	P.M. 6		
22	A.M. 6	6.96	
	P.M. 6		
23	A.M. 4	6.96	
	P.M. 8		
24	A.M. 8	6.96	
	P.M. 6		●— 2 P.M.
25	A.M. 6	6.96	●—10 A.M.
	P.M. 8		
26	A.M. 4	6.96	
	P.M. 6		
27	A.M. 6	6.96	
28	A.M. 4	11.6	
	P.M. 6		
29	A.M. 4	11.6	
	P.M. 4		
30	A.M. 4	11.6	
	P.M. 4		
31	A.M. 4	11.6	
	P.M. 4		
Apr. 1	A.M. 4	11.6	
	P.M. 4		
2	A.M. 4	11.6	Menstruation—(Apr. 2 to 7)
	P.M. 4		
3	A.M. 4	11.6	
	P.M. 4		
4	A.M. 4	11.6	
	P.M. 4		
5	A.M. 4	11.6	
	P.M. 4		
6	A.M. 4	11.6	
	P.M. 6		
7	A.M. 4		
	P.M. 4	11.6	°— 8 P.M. °—11 P.M.
8	A.M. 4		
	P.M. 4	11.6	°— 7 P.M.

uary, 1937, until September, 1940 (forty-four months), twenty-five grand mal and 181 petit mal seizures were recorded.

September, 1940, dilantin sodium was started in combination with phenobarbital. From this date until March 30, 1941 (six months), the attacks lessened and there were only three grand mal and nineteen petit mal seizures recorded.

March 31, 1941, when I first saw the patient, crotalin solution intramuscularly was begun for its nonspecific protein reaction (soil alteration).

Weichardt[17], one of the fathers of immunology, explained the nonspecific protein reaction as a cell-stimulating and plasma-activating effect, and, in a personal letter to me under date of November 13, 1925, in referring to an article of mine published September 16, 1925, states: "I see from your article on 'Nonspecific Therapy in Sensitization Diseases' in the

TABLE II. URINARY pH AND RECORD OF SEIZURES (Continued)
March 14, 1944-April 24, 1944

Date 1944	1st A.M. or other hour specimen Urinary pH	Total Amount taken Daily in 3 doses, after meals.† Gms.	Record of Seizures and Comment
Apr. 9	A.M. 4	11.6	○—10:30 A.M.
	P.M. 4		
10	A.M. 4	11.6	
	P.M. 4		
11	A.M. 4	11.6	
	P.M. 4		
12	A.M. 4	11.6	●— 8 A.M.
	P.M. 6		
13	A.M. 4	11.6	●— 7:45 A.M.
	P.M. 5		●— 6 P.M.
14	A.M. 4	11.6	●—10 A.M.
	P.M. 6		
15	A.M. 4	11.6	
	P.M. 4		
16	A.M. 4	11.6	
	P.M. 4		
17	A.M. 4	11.6	
	P.M. 4		
18	A.M. 4	11.6	
	P.M. 4		●— 2 P.M.
19	A.M. 4	11.6	
	P.M. 4		
20	A.M. 4	11.6	
	P.M. 4		
21	A.M. 4	11.6	
	P.M. 4		
22	A.M. 4	11.6	
	P.M. 4		
23	A.M. 4	11.6	
	P.M. 4		○— 3 P.M.
24	A.M. 4	11.6	
	P.M. 4		

†*d*-Glutamic Acid
Hcl. Caps. 0.58 Gm. each (Lederle)

Summarized deduction (Table II): *d*-Glutamic Acid Hydrochloride in capsules of 0.58 gm. each were given in three daily doses, totaling in amounts ranging from 4.6 to 11.6 grammes per day from March 14 to April 24, 1944.

A urinary pH of 5 or above occurred on twenty days during this period of forty-two days, 47.6 per cent of the days.

One menstrual period occurred during these forty-two days and the pH of the urine was above 4 only once, approximately 0.5 per cent of the days during menstruation. During this menstruation (April 2 to 7), two petit mal seizures occurred, both on the last day of the menstrual period.

No "hazy" attacks or convulsions occurred.

New York Medical Journal and Record that you have earlier turned in at the right path."

Starkenstein[16] had also shown in 1919 that alteration of the permeability of cell membranes was an important factor in the nonspecific protein reaction. Peterson[9], quoting the findings of both of these investigators, refers to the alterative effect of nonspecific protein reactions on enzymes[9], and Kolmer[6], discussing one of my papers, pointed to the possible effect on colloidal modification of nonspecific protein reactions.

Essex and his associates[4], in studying the physiological action of crotalin, conclude its effect is largely due to peripheral vascular dilatation. Recently, Seyle[11], Code[2], Dragstedt[3], Landis[7], and others all have stressed the alteration of cell permeability in anaphylactic shock and allergy.

TABLE III. URINARY pH AND RECORD OF SEIZURES
April 25, 1944–May 8, 1944

Date 1944	1st A.M. or other hour specimen. Urinary pH	Total Amount Taken Daily in 5 Doses, After Meals.† Gms.	Record of Seizures and Comment
Apr. 25	A.M. 4	10.0	*Note change* to Natural Dextrorotatory Glutamic Acid Tablets (P.D. & Co.), for 14 days.
	P.M. 8		
26	A.M. 4	10.0	
	P.M. 8		
27	A.M. 6	10.0	
	P.M. 6		
28	A.M. 4	10.0	
	P.M. 6		
29	A.M. 6	10.0	
	P.M. 4		
30	A.M. 4	10.0	
	P.M. 8		
May 1	A.M. 8	10.0	Menstruation—
	P.M. 6		(May 1 to 5) °—5 P.M.
2	A.M. 6	10.0	
	P.M. 6		
3	A.M. 4	10.0	
	P.M. 4		°—10 P.M.
4	A.M. 4	10.0	
	P.M. 4		
5	A.M. 4	10.0	
	P.M. 4		
6	A.M. 4	10.0	
	P.M. 4		
7	A.M. 4	10.0	
	P.M. 4		
8	A.M. 4	10.0	
	P.M. 4		•— 4 P.M. •—6 P.M.

†Natural Dextrorotatory Glutamic Acid *Tablets,* 0.5 Gm. each (P.D. & Co.)

Summarized Deductions (Table III): Natural Dextrorotatory Glutamic Acid *tablets* of 0.5 gm. each were started. (The tablets, instead of the larger 0.58 gm. capsules, seemed easier to take.) These were taken, 10 grammes per day in three divided doses from April 25 to May 8, 1944.

A urinary pH of 5 or above was present on eight of the fourteen days, 57 per cent of the days, when the tablets were being used.

A menstrual period occurred May 1 to 6, during which two petit mal attacks occurred, on May 1 and May 3, respectively. Two "hazy" attacks followed on May 8.

While the combined crotalin-dilantin-phenobarbital therapy controlled the major seizures in this patient, the petit mal type continued, even when lessened in frequency and, at times, in severity. From March 31, 1941, to December 1, 1944 (forty-four months), under anticonvulsant medication orally and crotalin intramuscularly, *no major seizures* occurred. The petit mal seizures were also lessened in frequency and many of them were described as a "haziness" without, as her family often thought, loss of consciousness. While from March 30, 1941, to November 20, 1943 (thirty-two months), prior to the start of glutamic acid medication, there were no convulsions, there occurred as recorded a total of eighty-six petit mal attacks and forty-eight "hazy" manifestations.

With the absence of major attacks for forty-four months but with the continuance of the petit mal type, even though lessened in number, this patient, through her intelligent co-operation, seemed an appropriate one in whom to use glutamic acid after the method suggested by Price, Waelsch and Putnam.[10] Accordingly, from November 20, 1943, to November 20, 1944, glutamic acid in one form or another of its two racemized forms, or dextrorotatory glutamic acid, was administered in various amounts in addition to dilantin sodium orally, 4½ grains daily, and crotalin solution intramuscularly, gr. 1/75, at bi-weekly intervals. A part of the time ½

grain of phenobarbital was also taken once a day. During this one-year period (November 20, 1943, to November 20, 1944) a total of thirty-one petit mal attacks and thirty-nine "hazy" manifestations occurred, which was about half the number recorded the previous year.

EFFECT OF GLUTAMIC ACID ON THE URINARY PH AND ON THE PETIT MAL TYPE OF SEIZURES

The patient made her own daily urinary pH determinations with "Alk-acid" test paper, matched with a colorimetric scale, both of which were supplied by the Fisher Scientific Company of Pittsburgh and St. Louis.

This method of recording the pH has been reported to be quite satisfactory and uniformly accurate as a universal indicator for hydrogen ion concentration. We have checked sixty-two of these colorimetric determinations against accurate electric potential determinations. This check has shown the relative degree of acidity to be approximately within a ½ pH unit, when compared with the electric potential determination.

For more detailed and accurate interpretation of the effect of glutamic acid on the urinary pH and petit mal seizures, a study and analysis of the daily records is submitted in the five accompanying tables.

SUMMARY OF FINDINGS RECORDED IN THE TABLES

Glutamic acid in four forms was administered, and the daily amount given recorded, to a female adult epileptic patient who had been rendered free from major (convulsive) seizures with anticonvulsant medication orally and crotalin intramuscularly for forty-four months, but in whom the petit mal attacks were only slightly affected and tended to recur, especially at or near the menstrual period. The pH of the urine was determined and recorded on arising each morning, and a part of the time also at night, for one year. The petit mal seizures and so-called "hazy" attacks are also noted in the five tables

TABLE I records the daily use of *dl*-glutamic acid hydrochloride, in capsule form, in varying amounts ranging from 1.5 gm. to 4.5 gm. daily. During this period of 114 days a 4 pH of the urine was present on fifty-nine days, or 52 per cent of the time. During these 114 days on *dl*-glutamic acid hydrochloride four petit mal attacks and twenty-one "hazy" manifestations occurred.

TABLE II and TABLE IV record the daily use of *d*-glutamic acid hydrochloride, in capsule form, in daily amounts ranging from 4.64 gm. to 11.6 gm. During these periods of 121 days a 4 pH of the urine was present on eighty-nine days, or 73 per cent of the time. In these 121 days, eleven petit mal seizures and eleven "hazy" manifestations occurred.

TABLE III records the daily use of natural dextrorotatory glutamic acid, in tablet form (Parke, Davis & Co.) in the amount of 10 gm. per day for fourteen days. During this two-week period, a 4 pH of the urine was present on six of the fourteen days, or 43 per cent of the time. Two petit mal attacks and two "hazy" manifestations occurred.

TABLE IV. URINARY pH AND RECORDS OF SEIZURES
May 9, 1944—July 28, 1944

Date 1944	1st A.M. or other hour specimen. Urinary pH	Total Amount Taken Daily in 5 Doses, After Meals.† Gms.	Record of Seizures and Comment
May 9	A.M. 6	11.6	*Note return* to d-Glutamic Acid Hydrochloride capsules, and increased daily amount taken.
	P.M. 4		
10	A.M. 4	11.6	
	P.M. 4		
11	A.M. 4	11.6	
	P.M. 4		
12	A.M. 4	11.6	●—8:15 A.M.
	P.M. 4		
13	A.M. 4	11.6	●—6 P.M.
	P.M. 4		
14	A.M. 4	11.6	●—9:15 A.M. ●—10:30 A.M.
	P.M. 4		
15	A.M. 4	11.6	
	P.M. 4		
16	A.M. 4	11.6	
	P.M. 4		
17	A.M. 4	11.6	
	P.M. 4		
18	A.M. 4	8.7	
	P.M. 4		
19	A.M. 4	8.7	
	P.M. 4		
20	A.M. 4	8.7	
	P.M. 4		
21	A.M. 4	8.7	
	P.M. 4		
22	A.M. 4	8.7	
	P.M. 4		
23	A.M. 4	8.7	
	P.M. 4		
24	A.M. 4	8.7	
	P.M. 4		
25	A.M. 4	8.7	
	P.M. 4		
26	A.M. 4	8.7	
	P.M. 4		
27	A.M. 4	8.7	Menstruation— (May 27 to 31)
	P.M. 4		
28	A.M. 4	8.7	
	P.M. 4		
29	A.M. 4	8.7	
	P.M. 4		
30	A.M. 4	8.7	
	P.M. 4		
31	A.M. 4	8.7	
	P.M. 4		
June 1	A.M. 4	8.7	
	P.M. 4		
2	A.M. 4	8.7	
	P.M. 4		
3	A.M. 4	8.7	
	P.M. 4		
4	A.M. 4	8.7	
	P.M. 4		
5	A.M. 5	5.22	
	P.M. 5		
6	A.M. 4	5.22	
	P.M. 4		
7	A.M. 4	5.22	
	P.M. 4		
8	A.M. 4	5.22	
	P.M. 4		
9	A.M. 4	5.22	
	P.M. 4		
10	A.M. 4	8.7	○— 9 A.M. ○— 6 P.M.
	P.M. 4		
11	A.M. 4	5.8	○—2 P.M.
	P.M. 4		
12	A.M. 4	5.8	
	P.M. 4		
13	A.M. 4	5.8	
	P.M. 4		
14	A.M. 4	5.8	
	P.M. 4		
15	A.M. 4	5.8	○—10 A.M.
	P.M. 4		
16	A.M. 4	5.8	○—10 A.M. ○—2 P.M.
	P.M. 4		
17	A.M. 4	5.8	
	P.M. 4		
18	A.M. 4	5.8	
	P.M. 4		

TABLE IV. URINARY pH AND RECORD OF SEIZURES (Continued)

May 9, 1944-July 28, 1944

Date 1944	1st A.M. or other hour specimen Urinary pH	Total Amount Taken Daily in 3 Doses, after Meals.† Gms.	Record of Seizures and Comment
June 19	A.M. 4	5.8	
	P.M. 4		
20	A.M. 4	5.8	
	P.M. 4		
21	A.M. 5	5.8	
	P.M. 4		
22	A.M. 4	5.8	
	P.M. 4		
23	A.M. 4	5.8	Menstruation—
	P.M. 4		(June 23 to 27)
24	A.M. 4	5.8	
	P.M. 4		
25	A.M. 4	5.8	°— 7:30 A.M.
	P.M. 4		
26	A.M. 4	5.8	
	P.M. 4		
27	A.M. 4	5.8	
	P.M. 4		
28	A.M. 4	5.8	
	P.M. 4		
29	A.M. 4	5.8	
	P.M. 4		
30	A.M. 4	5.8	
	P.M. 4		
July 1	A.M. 4	5.8	
	P.M. 4		
2	A.M. 4	5.8	
	P.M. 4		
3	A.M. 6	5.8	
	P.M. 4		
4	A.M. 4	5.8	
	P.M. 4		
5	A.M. 4	5.8	
	P.M. 4		
6	A.M. 4	5.8	
	P.M. 4		
7	A.M. 4	5.8	
	P.M. 4		
8	A.M. 4	5.8	
	P.M. 4		
9	A.M. 4	5.8	
	P.M. 4		
10	A.M. 4	5.8	
	P.M. 4		
11	A.M. 4	5.8	
	P.M. 4		
12	A.M. 4	5.8	
	P.M. 4		
13	A.M. 6	5.8	
	P.M. 4		
14	A.M. 4	5.8	
	P.M. 4		
15	A.M. 4	5.8	
	P.M. 4		
16	A.M. 6	5.8	
	P.M. 4		
17	A.M. 4	5.8	
	P.M. 4		
18	A.M. 4	5.8	
	P.M. 4		
19	A.M. 4	5.8	
	P.M. 4		
20	A.M. 5	5.8	
	P.M. 4		
21	A.M. 4	5.8	
	P.M. 4		Menstruation—
22	A.M. 4	8.12	(July 22 to 26)
	P.M. 8		
23	A.M. 6	5.8	
	P.M. 4		
24	A.M. 4	5.8	
	P.M. 4		
25	A.M. 4	5.8	
	P.M. 4		
26	A.M. 4	5.8	
	P.M. 6		
27	A.M. 6	5.8	
	P.M. 6		
28	A.M. 4	None	
	P.M. 6		

†*d*-Glutamic Acid Hcl. Caps. 0.58 Gm. each (Lederle)

Summarized Deductions (Table IV): *d*-Glutamic Acid in Hydrochloride in capsule form, 0.58 gm. each, were resumed, as the tablets in this racemized form were not being manufactured. The *d*-Glutamic Acid Hydrochloride was then continued for eighty days (May 9 to July 28, 1944), in doses of 5.22 gm., 5.8 gm. 8.7 gm. and 11.6 gm. daily in three equally divided doses of each. The varied amount taken daily was due to an effort to determine the smallest daily dose in order to maintain a urinary pH of 4, and to lessen the large number of capsules, for which the patient began to have a dislike.

During the eighty days, when the daily dosage was varied and reduced, the urinary pH was above 4 on twelve days out of the eighty, or 14.7 per cent of the days. Three menstrual periods occurred, during which time the urinary pH rose to 5 or above on two days only.

During these three menstrual periods while the *d*-Glutamic Acid Hydrochloride form was being used, over the eighty-day period there was only one petit mal attack which occurred during a menstrual period, and there were no "hazy" manifestations or convulsive seizures. (During the entire time when *d*-Glutamic Acid Hydrochloride was taken daily, 121 days, the pH of the urine was 5 or above on thirty-two days, 26 per cent of the days. (Tables II and IV together.)

There were no seizures in any form from May 14 to June 10, 1944. On June 10, 11, 15 and 16 petit mal attacks occurred which were independent of any menstrual influence. However, five days previous to the petit mal attack on June 10, *d*-Glutamic Acid Hydrochloride had been reduced in dosage from 8.7 to 5.22 grammes per day. The urinary pH remained at 4 for fifty-three days (June 5 to July 28) with exception of thirteen days, 24.5 per cent of the days. A daily amount of 5.8 gm. (15 capsules of 0.58 gm. each), were continued until July 28, when the patient ran out of the *d*-Glutamic form for twenty-four hours.

TABLE V records the daily use of "Glutan H-C-L"-Lederle (glutamic acid hydrochloride in capsule form), in amounts ranging from 3.888 gm. to 7.5 gm. per day. During 102 days of this time a 4 pH of the urine was present on forty-eight days, or 47 per cent of the time. Nine petit mal and ten "hazy" manifestations occurred. The patient then ran out of capsules from August 27 to September 8, 1944 (twelve days), and during the last five of these twelve days without any Glutan H-C-L 4 petit mal, no "hazy," attacks occurred and the pH of the urine rose to eight on one day, six on five days, five on one day and a pH of 4 was present only on four of the twelve days.

CLINICAL RESULTS

The administration of glutamic acid or one of its modifications or racemizations, used daily over a period of one year, in conjunction with crotalin intramuscularly and dilantin orally, was beneficial in lessening the frequency of petit mal type of seizures, and appreciably modifying their severity. The amount of acid administered was guided by a daily recording of the urinary pH in an effort to keep the hydrogen ion concentration (pH) below 5.

The petit mal type of seizure was little modified by the combined alterative and anticonvulsant action of crotalin and dilantin, although the convulsive seizures were absent for forty-four months. During the year (November 20, 1943, to November 20, 1944) when glutamic acid was added to the medication, petit mal seizures occurred twenty-seven times and there were so-called "hazy" symptoms recorded on forty-five days. It is of especial interest to note in Table V that with no glutamic acid

taken for twelve days the hydrogen ion concentration of the urine rose, after the third day, rather consistently each day to a 6 pH. Also, that during the last five days without acid, five petit mal seizures occurred. This increase of seizures with no glutamic acid followed a ten-week interval of entire freedom from any type of seizure. The previous year both types of petit mal seizures had occurred thirty-nine and fifty-one times, respectively.

During or near the time of a menstrual period throughout the year, minor forms of attacks were absent only three times. At these three periods a urinary pH of 5 or 4 was present. At each of the other nine periods of the year, petit mal or "hazy" manifestations appeared, and a urinary pH of 6, 7 or above was present.

Throughout the year (November 20, 1943, to November 20, 1944) while taking one or another form and amount of glutamic acid daily there occurred twenty-seven petit mal seizures (two at time of periods) and forty-five "hazy" manifestations (thirty-one of which occurred at time of periods), thus only fourteen "hazy" attacks occurred during the year while glutamic acid was being used and when the influence of the menstruation was not a factor.

COMMENT

It has been a general experience that anticonvulsants (bromide, phenobarbital, dilantin sodium) are of much value in modifying, to a greater or less extent, recurrent convulsive seizures (grand mal type of epilepsy).

The minor form, or petit mal type of seizure, has, however, rather uniformly been persistently resistant in many patients, to all forms of anticonvulsant medication.

The case report herewith submitted illustrates the usefulness of altering metabolism in an epileptic patient by biological intramuscular therapy which, in my experience, frequently has been a decided adjuvant to anticonvulsive treatment.

As is shown in the detailed data in this case report, and in the experience of Price and Waelsch[10], anticonvulsants have but a limited beneficial effect on petit mal type of seizures. The effect of crotalin solution intramuscularly in altering metabolism I have found for many years beneficial, at times alone, or combined with anticonvulsant therapy. However, even with the biological alterative effect of crotalin, the petit mal seizures are less influenced than the grand mal type of attack.

Naturally, a question arises: Do both forms of these clinical manifestations arise from a common cause—is there a trigger mechanism of common origin? In my clinical experience patients with predominantly minor manifestations of momentary lapses are the ones having a greater percentage of allergic backgrounds. The symptom complex of disturbed metabolism in allergic patients and in epileptics have much in common—including low gastric acidity with gastrointestinal disturbances (hypersensitivity) and, at times, an eosinophilia; frequently an alkaline urine.

TABLE V. URINARY pH AND RECORD OF SEIZURES
July 29, 1944–November 20, 1944

Date 1944	1st A.M. or other hour specimen. Urinary pH	Total Amount Taken Daily in 3 Doses, after meals.† Gms.	Record of Seizures and Comment
July 29	A.M. 4	3.888	*Note change* to stocked form of capsules, "Glutan" H-C-L.
	P.M. 4		
30	A.M. 4	5.832	
	P.M. 4		
31	A.M. 4	5.832	
	P.M. 4		
Aug. 1	A.M. 6	5.832	
	P.M. 4		
2	A.M. 4	5.832	
	P.M. 4		
3	A.M. 4	5.832	
	P.M. 4		
4	A.M. 4	5.832	
	P.M. 4		
5	A.M. 4	5.832	
	P.M. 4		
6	A.M. 4	5.832	
	P.M. 4		
7	A.M. 4	5.832	
	P.M. 4		
8	A.M. 4	5.832	
	P.M. 4		
9	A.M. 4	5.832	
	P.M. 4		
10	A.M. 4	5.832	
	P.M. 4		
11	A.M. 4	5.832	
	P.M. 4		
12	A.M. 4	5.832	
	P.M. 4		
13	A.M. 4	5.832	
	P.M. 4		
14	A.M. 4	5.832	
	P.M. 4		
15	A.M. 4	5.832	
	P.M. 4		
16	A.M. 4	5.832	
	P.M. 4		
17	A.M. 4	5.832	Menstruation—
	P.M. 8		(Aug. 17 to 21) *Soda bicarbonate for indigestion
18	A.M. 8*	5.832	
	P.M. 4		
19	A.M. 4	5.184	
	P.M. 4		
20	A.M. 4	5.184	
	P.M. 4		
21	A.M. 4	3.888	
	P.M. 4		
22	A.M. 5	3.888	
	P.M. 4		
23	A.M. 4	3.888	
	P.M. 5		
24	A.M. 4	3.888	
	P.M. 5		
25	A.M. 5	2.916	
	P.M. 4		
26	A.M. 5	2.916	
	P.M. 6		
27	A.M. 6	None	No Glutamic capsules from Aug. 27 to Sept. 8
	P.M. 8	"	
28	A.M. 4		
	P.M. 4	"	
29	A.M. 4		
	P.M. 4	"	
30	A.M. 4		
	P.M. 4	"	
31	A.M. 6		
	P.M. 6	"	
Sept. 1	A.M. 6		
	P.M. 6	"	
2	A.M. 6		
	P.M. 6	"	
3	A.M. 4		°—11 A.M.
	P.M. 6	"	
4	A.M. 4		°— 9:30 A.M.
	P.M. 4	"	°— 7 P.M.
5	A.M. 6		°—1:30 P.M.
	P.M. 4		

TABLE V. URINARY pH AND RECORD OF SEIZURES (Continued)
July 29, 1944-November 20, 1944

Date 1943	1st A.M. or other hour specimen. Urinary pH	Total Amount Taken Daily in 3 Doses, after Meals.† Gms.	Record of Seizures and Comment
Sept. 6	A.M. 5	"	
	P.M. 5		○— 2 P.M.
7	A.M. 4	"	
	P.M. 4		
8	A.M. 4	3.888	
	P.M. 4		●— 8 P.M.
9	A.M. 4	5.832	
	P.M. 4		
10	A.M. 4	5.832	●—11 A.M.
	P.M. 4		
11	A.M. 4	3.888	
	P.M. 4		
12	A.M. 4	5.832	
	P.M. 8*		*Ate tomatoes
13	A.M. 4	5.832	
	P.M. 5		
14	A.M. 4	5.832	
	P.M. 4		
15	A.M. 4	5.832	Menstruation—
	P.M. 4		Sept. 15 to 19
16	A.M. 4	5.832	
	P.M. 6		
17	A.M. 6	5.832	●—11:30 A.M.
	P.M. 6		
18	A.M. 4	3.888	
	P.M. 4		
19	A.M. 4	5.832	
	P.M. 4		
20	A.M. 4	5.832	
	P.M. 4		
21	A.M. 4	5.832	
	P.M. 4		
22	A.M. 4	5.832	
	P.M. 4		●— 2:30 P.M.
23	A.M. 4	5.832	
	P.M. 4		
24	A.M. 4	5.832	
	P.M. 4		●— 2 P.M.
25	A.M. 4	5.832	
	P.M. 4		
26	A.M. 4	5.832	
	P.M. 4		
27	A.M. 4	5.832	
	P.M. 6		
28	A.M. 4	5.832	
	P.M. 8		
29	A.M. 4	5.832	
	P.M. –		
30	A.M. 4	5.832	
	P.M. 4		
			Note: There had been no seizures from June 25, a petit mal while in Maine on vacation, until Sept. 3 (72 days), at home after 17-hour auto trip (2 A.M. to 7 P.M.), *and no Glutamic Acid Capsules from Aug. 27 to Sept. 8, 1944!*
Oct. 1	A.M. 4	5.832	
	P.M. 4		
2	A.M. 4	5.832	
	P.M. 4		
3	A.M. 4	5.832	
	P.M. 8		○— 6:30 P.M.
4	A.M. 4	5.832	
	P.M. 4		
5	A.M. 4	5.832	
	P.M. 6		●— 6 P.M.
6	A.M. 5	5.832	
	P.M. 4		
7	A.M. 4	3.888	
	P.M. 8		●— 2:30 P.M.
8	A.M. 4	2.592	
	P.M. 4		
9	A.M. 6	2.592	
	P.M. 4		○— 7 P.M.
10	A.M. 4	2.592	
	P.M. 6		
11	A.M. 6	1.296	
	P.M. 5		
12	A.M. 4	None	Menstruation—
	P.M. 8		(Oct. 12 to 16)

TABLE V. URINARY pH AND RECORD OF SEIZURES (Continued)
July 29, 1944-November 20, 1944

Date 1944	1st A.M. or other hour specimen. Urinary pH		Total Amount Taken Daily in 3 Doses, after Meals.† Gms.	Record of Seizures and Comment
Oct. 13	A.M.	8	"	
	P.M.	8	"	
			"Glutan" caps. increased to 0.5 Gm. each	
14	A.M.	4	6.0	
	P.M.	4		
15	A.M.	4	6.0	
	P.M.	4		
16	A.M.	4	6.0	
	P.M.	4		
17	A.M.	4	6.0	
	P.M.	4		
18	A.M.	4	6.0	
	P.M.	4		○— 1:30 P.M.
19	A.M.	4	6.0	
	P.M.	4		
20	A.M.	4	6.0	
	P.M.	4		
21	A.M.	4	6.0	
	P.M.	6		
22	A.M.	5	6.0	
	P.M.	4		
23	A.M.	4	6.0	
	P.M.	5		
24	A.M.	4	6.0	
	P.M.	6		
25	A.M.	5	6.0	
	P.M.	6		○— 7 P.M.
26	A.M.	4	6.0	
	P.M.	4		○—11 P.M.
27	A.M.	4	6.0	
	P.M.	4		
28	A.M.	4	6.0	
	P.M.	4		
29	A.M.	4	6.0	
	P.M.	4		●— 1 P.M.
30	A.M.	4	7.0	
	P.M.	6		
31	A.M.	4	7.5	
	P.M.	4		
Nov. 1	A.M.		7.5	
	P.M.			
2	A.M.		7.5	
	P.M.			
3	A.M.		6.0	
	P.M.			
4	A.M.		7.5	
	P.M.			
5	A.M.		7.5	
	P.M.			
6	A.M.		7.5	
	P.M.			
7	A.M.		7.5	
	P.M.			
8	A.M.		7.5	
	P.M.			
9	A.M.		6.0	
	P.M.			
10	A.M.		6.0	
	P.M.			
11	A.M.		6.0	
	P.M.			
12	A.M.		7.5	
	P.M.			
13	A.M.		7.5	
	P.M.			
14	A.M.		7.5	
	P.M.			○— 6 P.M.
15	A.M.		7.5	
	P.M.			
16	A.M.		6.0	
	P.M.			
17	A.M.		6.0	
	P.M.			
18	A.M.		4.0	
	P.M.			
19	A.M.		6.0	
	P.M.			●— 8 P.M.
20	A.M.		7.5	
	P.M.			

†Glutamic Acid Hcl. Caps. 0.324 Gm. each. (Lederle)

Summarized Deductions (Table V): July 29, 1944, "Glutan" (Lederle), i.e., Glutamic Acid Hydrochloride *capsules* of 0.324 mgm. each were started. This form of Glutamic Acid Hydrochloride is regularly stocked and marketed for use in hydrochloric acid deficiency. I was interested to compare it with the *dl*-Glutamic and *d*-Glutamic Acid, and with the natural dextrorotatory form of glutamic acid, since they are less expensive than the racemized forms of glutamic acid.

"Glutan" capsules in daily amounts ranging from 3.888 gms. to 7.5 gms. were given for 102 days. A urinary pH of 5 or above, during this time, was present on fifty-four days, or 53 per cent of the time.

Three menstrual periods occurred during the 102 days "Glutan" capsules were being taken, no period having occurred during the twelve days the patient was without medication. During these three menstrual periods, the urinary pH was 5 or above one day during each period, and only one "hazy" manifestation occurred. However, after seven days without any glutamic medication, four petit mal seizures occurred on four successive days.

It is of special note that while the patient was vacationing in Maine, from June 7 to September 1, no seizures occurred except one petit mal type of attack June 25, during a menstrual period when the *d*-Glutamic acid hydrochloride capsules were still being used. She passed through the menstrual periods of July and August with no attacks, during which time she took *d*-Glutamic acid by hydrochloride capsules for eighty days and then began the "Glutan" capsules, (Tables IV & V), for 114 days, which completes the record for one year.

The tendency for petit mal symptoms to appear or be more aggravated at menstrual periods in the female, and at full moon in males (lunar month) is a common observation in various forms of allergy as well as in patients with petit mal types of epilepsy.

The beneficial effect of glutamic acid in lowering the pH of the urine in epilepsy as illustrated in this detailed case report, and the fact that menstruation, even when the patient is taking glutamic acid, often causes an increase in petit mal seizures, raises the question as to whether endocrine dysfunction may be less of a factor in the etiology of petit mal, than the increase of the hydrogen ion concentration (pH) of the urine during menstruation.

Finally, grand mal may result from a vascular sensitivity as suggested by various investigators, through an increased vascular permeability with an edema of the cerebral cortex and surrounding tissues, which may be a possible seat of the so-called "shock organ," while petit mal may result more from an altered immunologic (allergic) response as shown by a decreased hydrogen ion concentration of the urine.

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THE STUDY OF BRONCHIAL ASTHMA IN A GENERAL HOSPITAL

With a Statistical Report of 200 Cases

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BRONCHIAL asthma, its related conditions and complications, is responsible for an enormous morbidity in the Army. A survey of the recent literature on the subject reveals nothing new or startling. The most important of the newer writings, however, deal with the military aspects of bronchial asthma. In a survey of Allergy by French and Halpin[6] of the Fourth Service Command, covering a period from 1 November 1942 to 1 November 1943, it is disclosed that 8,139 allergic patients who were admitted to the hospital wards spent a total of 172,455 hospital days. This figure was approximately 10 per cent of the total hospital admissions in the Command for this period. Bronchial asthma was responsible for the greatest number of these admissions, as 5,447 patients, or 66.6 per cent, had this diagnosis. The scope and importance of allergy in the Army is further emphasized in papers by Crandall[5], Lieder[10], Hampton and Rand.[7]

The concept of allergy has increased our understanding and appreciation of the different agents which cause asthma. It has played an important role in the medical diagnosis of asthma and in the clinical differentiation of all who wheeze. As a result, the wheezing dyspnea of asthma may be more easily separated from many intrathoracic medical conditions. This includes such conditions as cardiac decompensation (cardiac asthma), fibroid tuberculosis, chronic bronchitis, aspirated foreign bodies, inflammations within the bronchi, Loeffler's syndrome, bronchial stenosis due to tumors, mediastinal tumors including neoplasms, substernal thyroid, persistent thymus, tuberculosis, aneurysms, trachio-bronchial glands, and Hodgkin's disease. On the basis of clinical history and physical examination, and complemented by laboratory studies and x-rays, little room for doubt is left as to the diagnosis of the type of wheezing being studied in the patient.

The disease, though chronic and rarely fatal in itself, is followed by pulmonary changes which ultimately incapacitate the soldier. These complications and sequelae can be prevented and symptomatic cure obtained if the medical officer is thoroughly aware of the facts and is so situated as to carry out the necessary studies and treatment with the view to the proper disposition of the asthmatic soldier.

For the purpose of clarity, the statistics in this report on the study of asthma in this general hospital, were governed largely by the allergic concept, and each case was evaluated on the basis of the following criteria: (1) definition of asthma; (2) classification; and (3) specific criteria for the diagnosis of allergic asthma.

Presented before the Oliver Chapter of The Association of Military Surgeons, 23 March 1945.

TABLE I. CLASSIFICATION OF BRONCHIAL ASTHMA[3]

Allergen Antibody Stimulus		EXTRINSIC	Allergen Demonstrable	Begins early in life. Family history positive. Other allergic manifestations common. Skin tests positive or allergen demonstrable by environmental control. Complete remission between attacks. No organic changes. Prognosis for relief and prevention of future attacks good. Seldom die of asthma. No effect on longevity.
			Allergen not Demonstrable	
.....				
Cholinergic Stimulus	H Substance Reaction in Bronchial Asthma	INTRINSIC		Begins around forty years of age. Family history usually negative. Other allergic manifestations uncommon. Skin tests negative. Allergen not demonstrable by environmental control. No complete remissions. Organic changes common. Prognosis for relief and prevention of future attacks—poor. Prognosis as to life—grave. Many die of asthma. Profound effect on longevity.
.....				
Unknown Stimulus				
		COMBINED EXTRINSIC and INTRINSIC	Primary extrinsic with intrinsic complications	Organic Functional
			Primary intrinsic with extrinsic complications	Organic Functional

DEFINITION

We define bronchial asthma as an affliction of the lower respiratory tract, characterized by recurring paroxysms of wheezing and dyspnea more pronounced in the expiratory phase, frequently associated with coughing and a sense of constriction in the chest, due to pathological and physiological changes of the bronchioles.

Asthma today is regarded by many as a manifestation of hypersensitivity of the bronchial tree. The cells of the bronchial mucous membrane have been conditioned to react in an abnormal manner when brought into contact with substances which are ordinarily harmless. The reaction and symptoms are the result of edema of the bronchial mucous membrance and the outpouring of secretion and its associated bronchospasm. It is possible that the edema occurs in an attempt to dilute the toxic material and prevent its formation on the surface or within the cell substance, and that the secretion is poured out to wash the irritant away. The mechanism of the bronchospasm is probably similar to spasm in any hollow viscus, and in asthma results in an attempt to dislodge the mucus plugs in the bronchioles which have been formed by the secretion and cellular debris.

CLASSIFICATION

Many classifications of bronchial asthma may be found in the literature. The one used at this hospital has been based on the knowledge of the pathology of asthma, the mechanism involved in the pathology, and finally the symptoms produced as a result of these pathologic changes. My own experiences and studies during the past fifteen years have convinced me that bronchial asthma has a definite pathology regardless of the etiologic classification. This opinion is based in a great measure on the observations of

the histology of experimentally induced hypersensitive reactions in man, which was reported in 1932 by Kline, Cohen and Rudolph.[8] Recently Cohen[3] classified bronchial asthma, and since it covers essentially the same points used in our classification, it is shown herewith in Table I.

SPECIFIC CRITERIA[2]

In making the diagnosis of allergic from nonallergic asthmatic patients, the following points were considered:

1. In over half of the soldiers who have asthma there are allergic manifestations in collaterals or antecedents. However, specific hypersensitiveness may not be transmitted and the asthmatic patient may have antecedents with eczema, with migraine, with vasomotor rhinitis as well as with bronchial asthma.

2. As a rule, the allergic soldier has more than one allergic manifestation. There may be combinations of asthma and hay fever, asthma and eczema, asthma and nonseasonal vasomotor rhinitis, occurring more often sequentially, but occasionally concurrently.

3. Symptoms usually start early in life, the onset past the age of fifty being relatively infrequent.

4. At the outset asthma is chiefly paroxysmal in character. Between attacks, for indefinite periods, the patient may be practically normal, presenting neither subjective nor objective symptoms. As the condition progresses, attacks follow more rapidly, and complications such as bronchitis or emphysema may eliminate all free intervals.

5. Acute asthmatic attacks are often preceded by allergic symptoms involving other systems or organs, by hay fever, vasomotor rhinitis, gastrointestinal disturbances or angioneurotic edema.

6. The most severe attacks usually occur at night while trying to sleep.

7. There is a tendency to periodicity in relation to the hour of the day or night, day of week or season of the year.

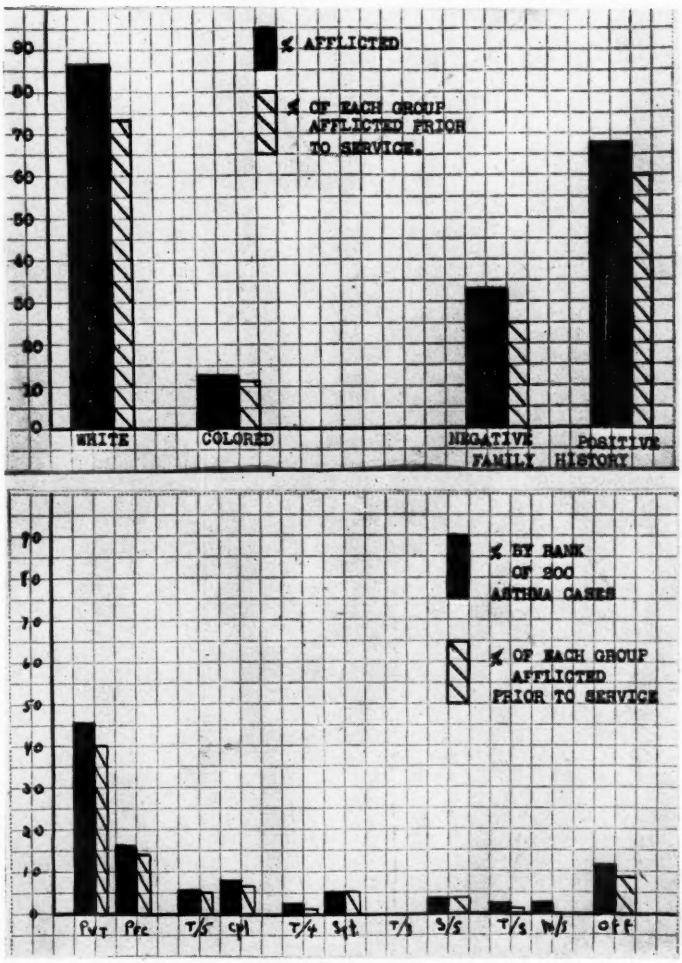
8. Orthopnea is frequently a prominent feature, even between paroxysms.

9. At first, emphysema is present only during the acute episodes; later it becomes a permanent feature in the physical findings.

10. Epinephrine in small doses will control the wheezing dyspnea in all cases except the most unusual ones.

11. If sputum is collected during or after an attack it may show Curschmann's spirals, Charcot-Leyden crystals, and frequently a high percentage of eosinophiles. A coincident blood and sputum eosinophilia is almost always a definite indication that allergy is the cause of the wheezing.

12. Positive skin tests help to identify the allergic soldier, but they do not necessarily make the etiologic diagnosis in all instances. Skin tests may err in two directions—frequently they are positive to allergens impossible to correlate with the clinical picture, and at times there are no skin reactions when the patient has symptoms from a particular



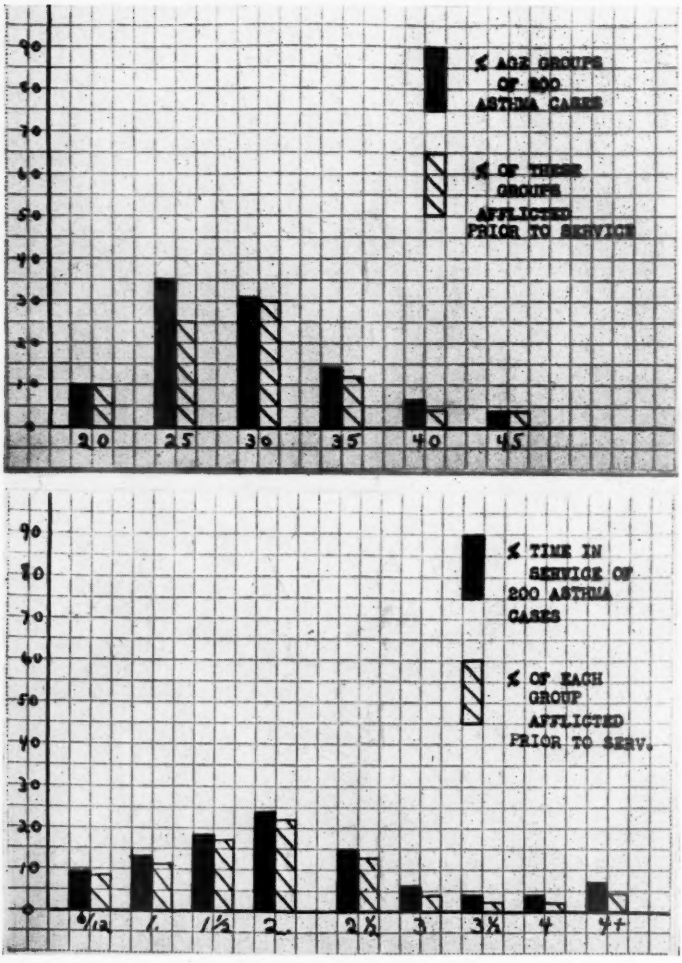
CHARTS 1 AND 2.

allergen. Positive skin tests to inhalants as a rule are clinically significant.

13. Finally, the patient with allergic asthma is chronically ill. One seldom dies from asthma, but there is an unusually high morbidity. If death does occur in the allergic group it is more often accidental, while the nonallergic, or intrinsic, asthmatics appear to have a definitely greater mortality.

STATISTICAL SURVEY OF 200 CASES

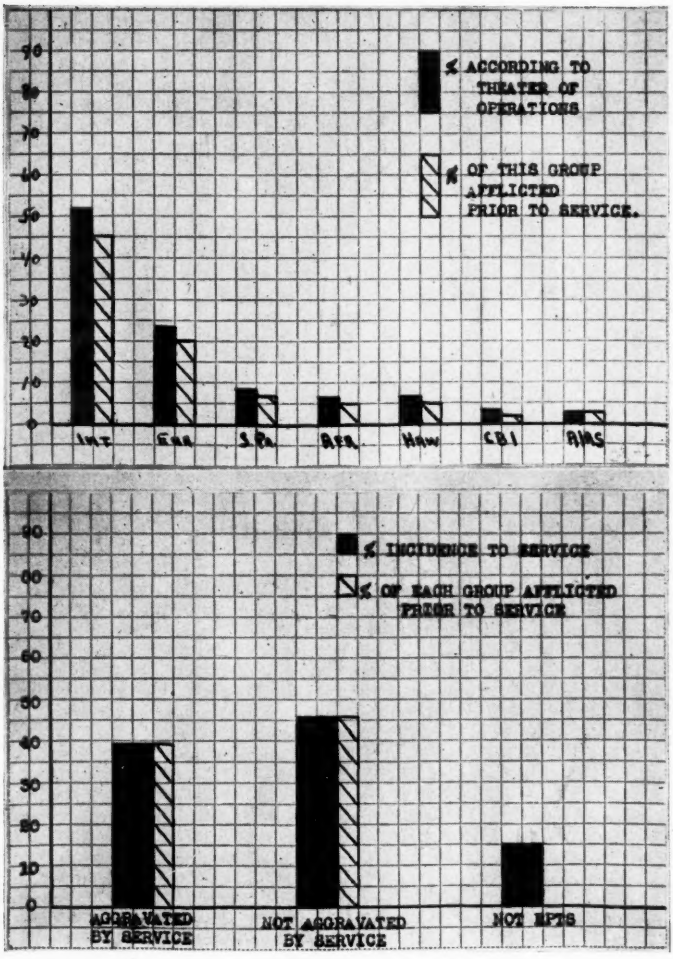
This report, from the Allergy Section at Oliver General Hospital, is a review of 200 consecutively hospitalized asthmatic patients. It reveals that



Charts 3 and 4.

exacerbations, invalidizations and hospitalizations in overseas theatres are common, and that patients are frequently returned to the Zone of Interior. Often patients who had mild or infrequent attacks of asthma in the States developed attacks of asthma almost immediately upon arriving in foreign theatres of war and were unable to carry on with any type of duty. The importance of understanding this situation and knowing the vagaries of asthma will help one to properly classify and avoid sending many soldiers overseas who may break down and have severe asthmatic attacks. In this report the following information was obtained:

Chart 1.—This chart reveals that 174 patients, or 87 per cent of the

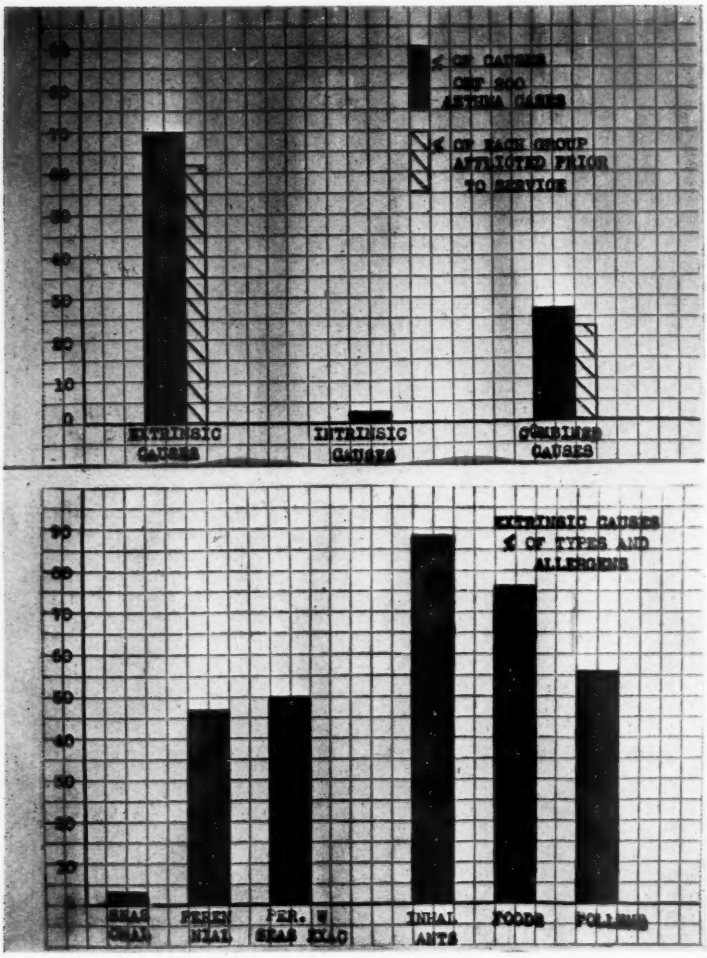


CHARTS 5 AND 6.

total, were white soldiers, and twenty-six patients, or 13 per cent, were negro soldiers. The family history was positive in 135 cases, or 67.5 per cent, and negative in sixty-five cases, or 32.5 per cent. There were no apparent differences in the onset or severity of the symptoms in either of these groups.

Chart 2. This chart reveals the distribution of asthma in the various grades in this series of 200 patients.

Chart 3. This chart points out the age range in soldiers with asthma. Twenty cases, or 10 per cent of the total, were either twenty years old or



Charts 7 and 8.

less; seventy cases, or 35 per cent, were in the twenty-five-year age group; sixty-four cases, or 43 per cent, were in the thirty-year age group; and twenty-eight cases, or 14 per cent, were in the thirty-five-year age group. One hundred and eighty-two soldiers, or 91 per cent of the total, were in the twenty- to thirty-five-year range, and this would be expected to be the case in military service. The age of onset of the asthma occurred frequently in childhood, and decreased rather rapidly after the age of thirty.[12]

Chart 4.—It is of interest to note in this chart that of the total number of asthmatics 79 per cent, or 158 patients, had less than two and one-half

years of service prior to their final disposition in the Army; that 14 per cent, or twenty-eight patients, had up to four years' service; and that 7 per cent, or fourteen patients, had over four years' service. This observation indicates that asthmatic persons break down rather rapidly and require disposition by the end of two and one-half years.

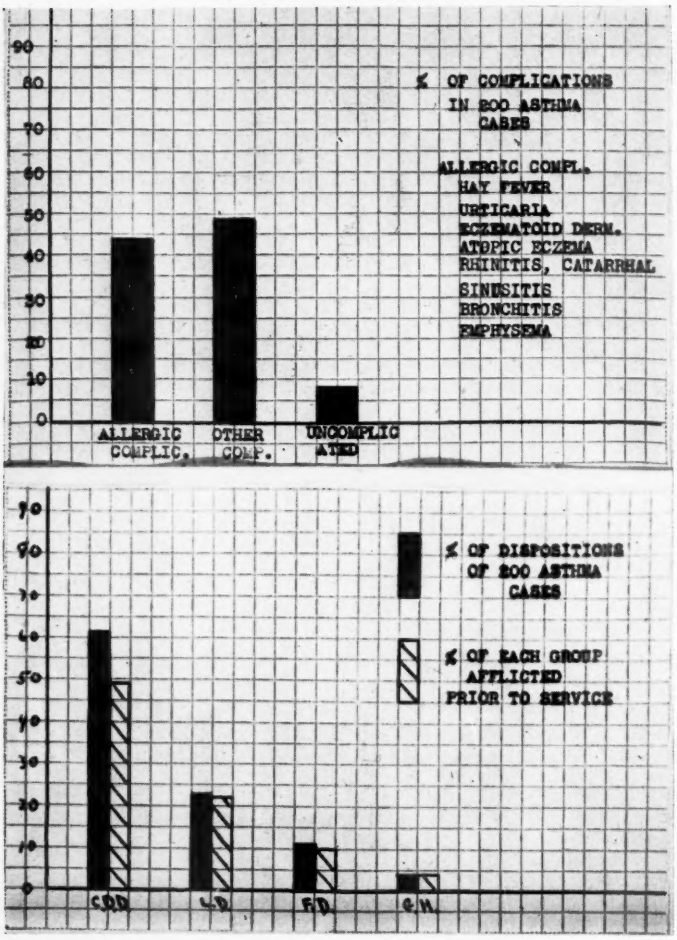
Chart 5.—In this chart we note that thirty cases had their initial attack of asthma in the service, and that 9 per cent of this group, or eighteen cases, had their first attack overseas. Of the total 200 cases, 48 per cent, or ninety-six patients, went overseas, and each soldier of this group was hospitalized overseas because of his asthma and required evacuation to the United States for study, treatment and final disposition.

Chart 6.—Although mobilization regulation MR 1-9[11] states that asthma of any degree is disqualifying for induction into the Army, 170 patients, or 85 per cent of this group, had the onset of their asthma prior to military service. Of the total group, thirty patients, or 15 per cent, had their initial attack of asthma incident to service, and seventy-eight cases, or 39 per cent, were aggravated by service, making a total of 108 patients, or 54 per cent, who had the onset or an aggravation of their asthma in the service.

Chart 7.—This chart reveals that the asthma was extrinsic in type in 140 cases, or 70 per cent; combined extrinsic and intrinsic in fifty-five cases, or 27.5 per cent; and intrinsic alone in five cases, or 2.5 per cent. These findings are in accord and conform to Table I of the classification described above.

Chart 8.—This chart shows that most of the extrinsic asthmatic soldiers were found to be skin sensitive to multiple inhalant allergens. Of the total, 166 cases, or 83 per cent, were sensitive to inhalants, including dust, feathers, molds, wool, cotton, kapok and tobacco. Of these patients, 112 were also sensitive to pollens, including both giant and dwarf ragweed, timothy, Bermuda grass, Johnson grass, redtop, orchard grass and careless weed. In addition, 154 of the patients, or 77 per cent, were sensitive to various food allergens, the most common being in the cereal, egg, milk and meat groups. The previous chart revealed the small number of purely intrinsic cases, and this group was sensitive by skin tests primarily to the upper respiratory bacteria.[4] The diagnosis of these cases was made largely by the history of repeated upper respiratory infections followed by asthmatic paroxysms. The combined extrinsic and intrinsic types were essentially a combination of the above, that is, they had positive skin tests and clinically verified sensitivity to inhalant and bacterial allergens. In some instances the extrinsic factor predominated, while in others the intrinsic factor predominated, with a greater or lesser degree of organic or functional complication.

Chart 9.—This chart and Table II present the associated allergies, complications and coexisting diseases included among these 200 soldiers. Of



CHARTS 9 AND 10.

the total, 184 patients, or 92 per cent, presented associated allergies, complications or coexisting diseases, and sixteen patients, or 8 per cent, were uncomplicated.

Chart 10.—The disposition of patients from a general hospital depends in a great measure on the requirements of the military service as well as on the physical condition of the soldiers. With the changing by the War Department of the physical requirements for limited duty, a number of asthmatics were discharged on a certificate of disability; however, when the manpower shortage became acute, some mild to moderate asthmatics were retained in service in limited duty capacities conforming to their physical abilities. Disposition was carefully evaluated for the 200 asth-

TABLE II. COEXISTING CONDITIONS

	Number	Per Cent
Hay fever	60	30.0
Sinusitis	18	9.0
Tonsillitis	17	8.5
Emphysema	14	7.0
Urticaria	10	5.0
Intestinal parasites	8	4.0
Catarrhal rhinitis	8	4.0
Bronchitis	7	3.5
Eczematoid, dermatitis	7	3.5
Atopic eczema	6	3.0
Nasopharyngitis	5	2.5
Malaria	5	2.5
Dermatitis	4	2.0
Conjunctivitis	2	1.0
Polypi	2	1.0
Gastric ulcer	2	1.0
Adenopathy	1	0.5
Periostitis	1	0.5
Bronchiectasis	1	0.5
Hematuria	1	0.5
Lung abscess	1	0.5
Neuritis	1	0.5
Pleurisy	1	0.5
Psychoneurosis	1	0.5
Rheumatic fever	1	0.5
	184	92.0%

TABLE III. TWO HUNDRED ASTHMATIC CASES

AS A CIVILIAN:		
1. Times hospitalized for asthma	0	0
2. Months lost because of asthma	580	2.9
AS A SOLDIER:		
1. Number of hospital admissions	1180	5.9
a. For asthma	810	4
b. For other than asthma	370	1.9
TOTAL MONTHS LOST DUE TO ASTHMA WHILE IN THE ARMY	797	3.98
BEFORE LEAVING STATES:		
1. Times relieved from duty due to asthma	220	1.1
2. Times hospitalized for asthma	70	.35
3. Months lost due to asthma	157	.78
WHILE OVERSEAS:		
1. Times relieved from duty due to asthma	570	2.85
2. Times hospitalized for asthma	210	1
3. Months lost due to asthma	640	3.2
TOTAL SERVICE IN MONTHS	6040	30.2
MONTHS OVERSEAS SERVICE	2410	12.05
MONTHS SERVICE IN STATES	3630	18.15

matic patients. Of these, as shown in Chart 10, twenty-three patients, or 11.5 per cent, were returned to full duty; forty-seven patients, or 23.5 per cent, were returned to limited duty; eight patients, or 4 per cent, were transferred to veterans' hospitals; and 122 patients, or 61 per cent, were discharged on a certificate of disability. In view of the relative frequency of exacerbations or aggravations of symptoms on overseas duty, for those who were being returned to a limited duty status it was recommended that they be placed on duty within the continental limits of the United States. It would appear from the foregoing data that an asthmatic soldier as a rule does poorly in military service. He is frequently invalided, requires frequent hospitalizations, as is shown in Table III, and after a relatively short period of duty more than half of them must be separated from the service. Conclusions drawn by Alford[1] in a recent article on asthma are as follows:

1. "Men with active bronchial asthma should not be inducted into the Army.
2. "Soldiers with bronchial asthma may be placed on nonstrenuous duty if:
   (a) Attacks are due to a single sensitivity for which rapid, adequate treatment is available;
   (b) Attacks are mild or infrequent, not preventing light duty;
   (c) The initial attack was overseas; and
   (d) The attack in the Army was a recurrence from childhood."

An additional report by Leopold[9] on asthmatics returning from overseas indicates that the greatest majority of soldiers continue to have asthma after their return to the States. This was true in 95.5 per cent of his group, and of the total group 31.5 per cent had the initial onset of their asthma overseas, and 68.5 per cent had a recurrence or aggravation of a preexisting asthma overseas. He considers hot and humid climates especially bad for asthma and believes that they were precipitating factors in his series of cases.

TREATMENT

Soldiers having acute, isolated attacks brought about by intermittent exposure to excitants, perhaps precipitated by overexertion, emotional disturbances, acute infections or fatigue, respond well to vasoconstrictor drugs, since chronic pathologic changes have not had time to become established in the lungs. Ephedrine in ⅜ gr. doses given by mouth in capsules may be sufficient for relief. Phenobarbital will counteract the nervousness and insomnia often produced by ephedrine and should be added; however, in many cases the barbiturates produce an obscure, insidious increase in the asthmatic symptoms, which may be masked for a time by the action of ephedrine. Hence, it is well to test the asthmatic patient with a small initial dose of the barbiturate. An aqueous solution of epinephrine, 1:100, sprayed into the mouth through a special nebulizer and inhaled into the bronchial tree is effective when available, and we have found this to be of definite value in a number of our patients.

We have employed combinations of caffeine citrate, ephedrine sulfate and phenobarbital, one-half grain of each, with considerable benefit. Aminophylline, 1:5 to 3 gr. tablets, repeated every three to four hours by mouth is an active antispasmodic drug, and has been especially beneficial in the intrinsic cases. For severe paroxysms, epinephrine by parenteral injection is our ranking therapeutic agent. Small doses, 0.1 to 0.3 c.c. of the 1:1,000 solution, are usually effective. Although as large a dose as 0.6 c.c. may be necessary, we have found it better to give repeated small doses every thirty minutes (0.3 to 0.5 c.c.).

When the asthma has become chronic, infection of the continuously edematous bronchial mucosa adds to the constriction, giving rise to bronchitis, emphysema and atelectasis. Under these circumstances, in addition to remedies already mentioned, expectorants, particularly iodides, give relief by thinning the thick, tenacious bronchial secretion. The saturated aqueous solution of potassium or sodium iodide may be given orally, 5 to

30 minims in water after meals. Small amounts of codeine may be required to control coughing. Morphine must not be used for patients with chronic asthma, as it frequently increases symptoms.

For status asthmaticus, aminophylline should be given intravenously very slowly, 3¾ to 7½ gr. diluted in 10 to 20 c.c. of saline.

Anoxia resulting from a prolonged attack is corrected by oxygen inhalations. Hypertonic solutions, such as 25 to 50 per cent glucose in amounts of 50 c.c. may be given intravenously to reduce bronchial edema.

All sources of continuous infection or irritation of the bronchial system, such as chronc sinusitis, must be given appropriate attention. Chronic infection of the pulmonary tissues, particularly bronchiectasis, if present, must be eradicated, if necessary, by surgical intervention. None of our patients required this treatment.

In all allergic soldiers multiple sensitization must be considered, as is indicated in the data. Drugs must therefore be used with caution, since the salicylates, coal-tar products, may aggravate an asthmatic tendency, or even precipitate an attack.

Belladonna, through its paralyzing effect upon bronchial nerve endings, may act to relax smooth muscle spasm, but at the same time it may dry the mucous surfaces and block the bronchi with thick mucus.

Calcium, histamine, histaminase, and potassium chloride alone have all been disappointing when tried for the relief of asthma, in this group of asthmatics.

CONCLUSION

The prognosis of bronchial asthma is notoriously uncertain. Asthma may manifest itself by a single attack, although this is unusual. It may continue for many years, or it may disappear only to recur years later. There are two significant facts regarding the prognosis of asthma, namely, that death during atacks is exceedingly rare, and the degree of disability is dependent largely upon the extent of the complications.

In the disposition of the allergic soldier, a board of medical officers has to consider the severity or constancy of the symptoms, the response to therapy, and the professional opinion of the attending medical officer. The ability of the patient with asthma and the degree of his incapacity have been seriously considered in all instances at this hospital. Reassignment would be advisable frequently if proper placement and allergic care could be continued. This type of disposition would of course be ideal, since both the soldier and the Army would profit mutually. However, in some cases the only correct procedure is to discharge the asthmatic soldier on a certificate of disability. The data presented above reveals no absolute standard which can be depended upon as to ultimate disposition. In the cases of bronchial asthma which we have discharged from the service we were governed in the main by the severity of symptoms and the fact that these symptoms were so severe that it was believed these men could no longer perform satisfactorily the duties required of a soldier in the Army.

When the physical manifestations of an allergic state have appeared, the offending substance must be discovered. If it is material that can be easily avoided, such as food that can be eliminated from the diet, the problem is simply solved. If the agent cannot be abolished, the affected soldier may be removed from the environment. This procedure is applicable only for the seasonal irritants, and this is not always possible in the Army. In many instances the asthmatic soldier may be successfully hyposensitized to the offending allergen, but here too the element of time does not always permit the complete fulfillment of this procedure, so that remedial measures must be employed in most instances.

SUMMARY

1. Bronchial asthma, its related conditions and complications, is responsible for an enormous morbidity in the Army. This fact is revealed by a number of recent surveys in the literature and by the data on 200 cases of bronchial asthma reported in this paper.

2. For the purpose of clarity, the statistics in this report on the study of the asthmatic condition of each soldier was governed largely by the allergic concept and each case was evaluated on the basis of a generally accepted definition of asthma, a recognized classification, and acceptable specific criteria for the diagnosis of allergic asthma.

3. The statistical findings brought to light the following facts:

(a) That 135 cases, or 67.5 per cent of the total of 200 cases, had a positive family history;

(b) That the age range of the soldiers with asthma in 182 cases, or 90 per cent, was from twenty to thirty-five years;

(c) That 158 cases, or 79 per cent, had less than two and one-half years' service prior to final disposition;

(d) That 170 cases, or 85 per cent, had the onset of their asthma prior to military service, and only thirty cases, or 15 per cent, had their initial attack incident to service;

(e) That 108 patients, or 54 per cent, had an overseas onset or aggravation of their symptoms;

(f) That 184 cases, or 92 per cent, had associated allergies, complications or coexisting diseases; and finally

(g) That 122 cases, or 61 per cent, were discharged on a certificate of disability; forty-seven cases, or 23.5 per cent, were returned to limited duty; twenty-three patients, or 11.5 per cent, were returned to full duty; and eight patients, or 4 per cent, were sent to veterans' hospitals.

4. In the cases of bronchial asthma which we have discharged from the service we were governed in the main by the severity of symptoms and the fact that these symptoms were so severe that it was believed that these men could no longer perform satisfactorily the duties required of a soldier in the Army.

(Bibliography on Page 276)

CARCINOMA OF THE LUNG WITH ASTHMATIC SYMPTOMS

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THE diagnosis of asthma as a rule is quite simple. Patients often report to your office with the diagnosis already made by friends or relatives, but the diagnosis of asthma is not always that simple, for there are many things which may produce a wheeze. After all, a wheeze is only an indication of a mechanical interference with respiration. The presence of râles in the chest in conjunction with a history of asthma, is not in itself proof of bronchial asthma. It has been said, "all that wheezes is not asthma," and it is well to keep this fact in mind when making a simple diagnosis of bronchial asthma.

Of all those things which may produce a mechanical wheeze in the bronchi, carcinoma of the lung is responsible in a small percentage of cases. In a series of seventy-five bronchogenic carcinoma cases studied by Overholt and Rumel, 38 per cent gave symptoms of dyspnea or wheezing.[2] The purpose of this paper is not to point out the diagnostic features of lung carcinoma, but to emphasize the fact that some of these bronchogenic carcinomas may follow the pattern of bronchial asthma. Four cases will be presented to illustrate this point.

CASE REPORTS

Case 1.—A man, aged fifty-two; chief complaint—asthma.

For fifteen years, this man had a nonproductive cough present both summer and winter. In May, 1936, this case was diagnosed as bronchial asthma, and a series of skin tests was made. A vaccine was prepared from the sputum, and he was treated for five months without benefit. A submucous resection was performed, and his teeth were removed.

While his complaint in the beginning was cough, he began to wheeze in January, 1937, and in May had his first acute attack of asthma. This attack lasted four days, and he was exceedingly short of breath and wheezed. Adrenalin was given and he coughed up bloody, gelatinous secretion. While this relieved the attack of asthma, the cough persisted.

He consulted another physician who made more vaccine. Adrenalin taken twice daily, controlled his wheezing, but did not control the coughing. His attacks of asthma became increasingly worse, and he lost forty pounds in weight. He became hoarse, and complained of substernal soreness.

He reported for consulation in November, 1937.

His family history was negative for allergy, and laboratory findings showed no eosinophils in the sputum. A few wheezing rales could be heard over the sternum, the apices were fairly clear, and breath sounds over the right midchest were difficult to elicit.

At the time he reported for consultation, no x-ray studies had ever been made of the chest, but when x-ray studies were made, the roentgenologist's report was as follows: "Diaphragms, heart, and mediastinum are within normal limits. The trachea is displaced to the right, indicative of some retraction of the right lung. The left lung fields appear fairly normal except for some slight increase in the vessel markings throughout, and evidence of some emphysema of the parenchyma.

On the right side there is a large increase in the right hilar shadow, extending into the right lower lobe, well out toward the periphery and down toward the diaphragm. There is very marked fibrosis in the region. It could be the result

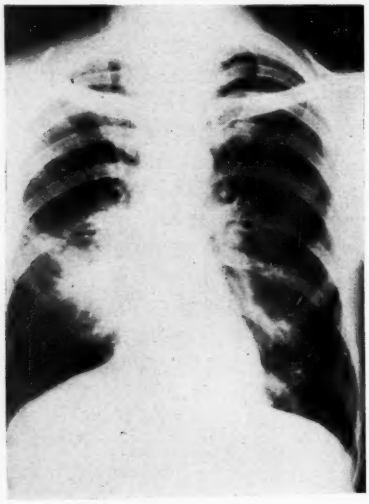

FIG. 1.

of either an old, healed abscess, or a neoplasm involving the bronchi in the region. It is probably the result of an old abscess which could be tuberculous." (Fig. 1).

Ten days later, this man died of pulmonary hemorrhage, and postmortem examination showed carcinoma of the right bronchus.

Case 2.—A woman, aged fifty-eight; chief complaint—asthma.

This patient could not fix the date when symptoms began, but believed that she experienced shortness of breath on exertion for the past four years. In 1938, a wheeze was noticed on exertion, and she consulted her physician who made a diagnosis of asthma, and recommended a change of climate. The wheezing gradually became worse, and shortness of breath persisted. One year later, she purchased an adrenalin spray, and this was used several times daily with help. Following the use of this spray, she would cough up a thick, yellowish secretion which gave relief. Later she coughed up blood-streaked sputum.

She reported for consultation in March, 1940.

Her family history and her own past history were negative for allergy, and there were no eosinophils in the sputum.

Wheezing râles were present in both respiratory phases, heard best over the midsternum, and atelectasis was suspected (Figs. 2 and 3).

The roentgenologist's report was as follows: "A very unusual, extensive, irregularly solid type of infiltration is shown extending into both lung fields. Some irregular annular zones of increased density are present which are bordered by hazy areas. The solid portions probably represent large metastatic nodes which produce atelectasis. Pleural changes are present at the bases which deform the costophrenic angle and sulci. No metastatic lesions are seen in the rib cage or the dorsal spine."

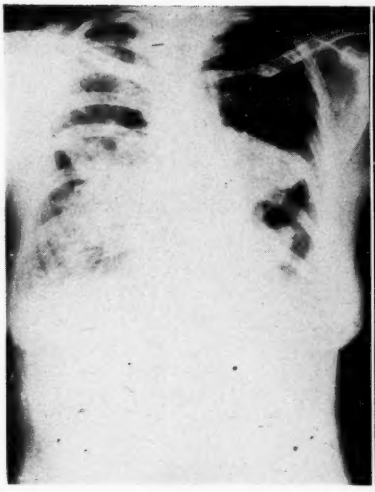

FIG. 2

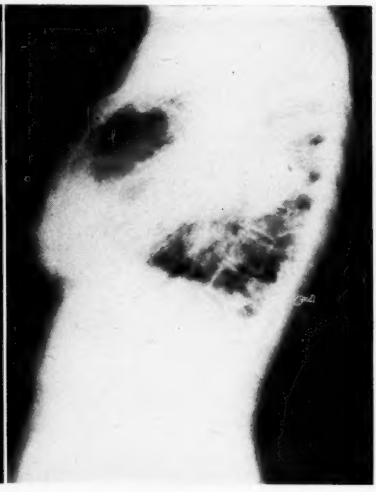

FIG. 3

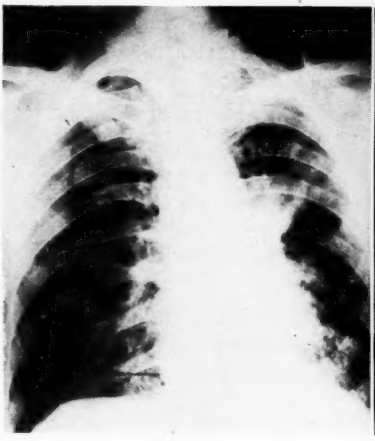

FIG. 4

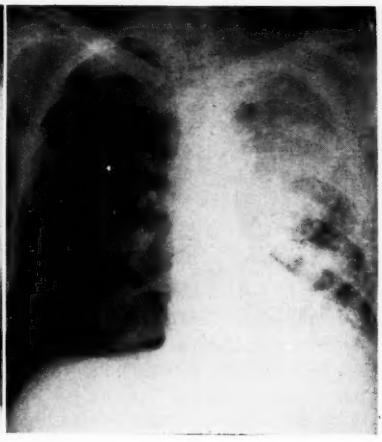

FIG. 5

This patient died in June, 1940, and postmortem examination showed carcinoma of the lung.

Case 3.—A man, aged fifty-six; chief complaint—asthma.

This patient gave a history of asthma for the past three years. He wheezed, was short of breath, and had a productive cough. The wheezing was worse when lying down, and with exertion.

In October, 1942, a series of skin tests had been made, and he was placed on a very restricted diet. While he thought he was better on the diet, he lost fifty pounds in weight in five months. He was advised by his physician to discontinue the diet, change climates, and in February, 1943, he came to Portland.

He reported for consultation in February, 1943.

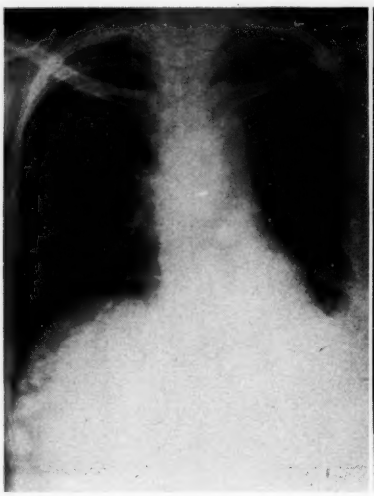

FIG. 6

FIG. 7

The family history was negative for allergy.

There was limited expansion on the left side, with dullness and distant breath sounds. Wheezing râles could be heard both anteriorly and posteriorly (Fig. 4).

The roentgenologist reported his findings as indicative of chronic pneumonitis, tuberculosis, or mycotic infection. Although the history and symptoms were somewhat suggestive of asthma, the findings suggested the possibility of bronchogenic carcinoma.

By June, 1943, he had lost sixty pounds, and was having chest pain. He noticed blood-streaked sputum, and complained of an obnoxious taste and odor to the sputum. Examination of the chest showed atelectasis of the left side, and x-ray findings at that time suggested strong indications of an extensive tuberculous involvement of the left lung (Fig. 5).

Bronchoscopic examination revealed a growth extending into the left main bronchus, biopsy of which proved it to be carcinomatous.

In July, 1943, the patient died.

Case 4.—A woman, aged fifty-six; chief complaint—asthma.

This patient's first attack of asthma followed a coronary disease in 1942. She was short of breath, and wheezed. One year later, a series of skin tests had been made, and vaccines administered without benefit.

She reported for consultation in May, 1944.

Her family history was negative for allergy.

There was a definite inspiratory wheeze, heard over the midchest. The x-ray studies showed typical fibrosis as seen in chronic asthma, but no well defined pathology in the chest. The vocal cords were examined and found to have a definite paralysis which did not open with inspiration, but appeared to have the reverse reaction and constricted during deep inspiration (Fig. 6).

X-ray examinations six months later showed marked retraction of the mediastinum to the left, and the trachea was markedly deviated. From the bronchoscopic examination one could see a stricture of the left bronchus (Fig. 7).

She became more dyspneic, the cough was productive, and sputum contained

mucopurulent material, but no blood. Substernal pains developed and she complained of constriction about her chest.

The final x-ray was taken in March, 1945, and the roentgenologist reported: Apices clear, increased markings of both lung fields. Mediastinum pulled to the left. Increased density of fifth interspace probably a metastatic lesion.

The patient had a sudden loss of weight and died in April, 1945.

The diagnosis was lung carcinoma.

These four patients did present definite symptoms of asthma, were diagnosed and treated as such, and some had relief with the use of asthmatic remedies. Carcinoma was not considered in the early phases because the symptoms were masked by the characteristic asthmatic wheeze. While some of these cases no doubt could have been diagnosed earlier if carefully examined, the diagnosis became evident as they progressed to their termination.

Carcinoma	*Asthma*
Usually no record of allergy in the past or family history.	History of allergy usually present.
Symptoms develop after forty-five years of age.	Symptoms develop before forty-five years of age.
Cough precedes the wheeze by several months.	Cough usually comes with or follows the wheeze.
Wheezing râles localized.	Wheezing râles generalized.
Diaphragm arched.	Diaphragm flattened.
No eosinophils in the sputum.	Eosinophils present.
Blood often in the sputum.	Blood seldom in the sputum.
Marked loss of weight and rapid downhill course.	Weight and course remain about the same.

Carcinoma of the lung may manifest itself in many ways, and the asthmatic syndrome is presented in a relatively large group of cases. Carcinomatous involvement of the lung is much more common than is usually believed. Some have reported as high as 18.5 per cent in all autopsies performed in one of the large general hospitals. In the Cleveland City Hospital, the lung is considered the second most frequent site of carcinoma, the stomach being the first.[1]

Carcinoma of the bronchus at first produces no symptoms or clinical signs, only a dry, irritating cough, but as the tumor increases in size, a segmental emphysema results. In this emphysematous stage, wheezing and asthmatic breathing make their appearance. Dyspnea and wheezing in the Overholt and Rumel series were found to be present in 38 per cent of bronchogenic carcinomas, and are considered early symptoms.[2]

It is in the stage of partial obstruction of the bronchus that one might make an erroneous diagnosis of asthma. Secretion which is produced adds to the asthmatic symptoms. As the tumor begins to break down, purulent sputum is noted, with occasional hemorrhages. In the last stage of atelectasis, the picture changes completely, and all symptoms of asthma then disappear.

Most cases of carcinoma of the lung are not diagnosed until it is too late for lobectomy. Surgeons have made great strides with encouraging

results, but if these patients are to be helped, we as allergists and internists must recognize symptoms early.

X-ray is often misleading in the early diagnosis of carcinoma of the lung. The clinical signs and history are far more important and all cases in which carcinoma is suspected should be bronchoscoped.

The differential diagnosis between allergic bronchial asthma and bronchogenic carcinoma is offeretl in the accompanying table:

CONCLUSIONS

Bronchogenic carcinoma may assume the pattern of asthma especially in the stage of partial obstruction with segmental emphysema. Therefore, the wheeze should be an early symptom of bronchogenic carcinoma.

Four cases are presented to illustrate the importance of differentiating asthma from lung carcinoma and some differential diagnostic points are given.

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ALLERGY TO TOBACCO SMOKE

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DETAILED accounts of allergy to tobacco smoke are lacking in the medical literature. A. Brown records his observed incidence as one per cent of asthmatics due to tobacco or tobacco smoke. He does not differentiate between the two. Vaughan cites allergic episodes in several individuals, apparently precipitated by exposure to tobacco smoke. He also outlines briefly a procedure for making tobacco smoke extract.

In the present study, the records of 370 consecutive allergic patients seen in private practice were studied. No note was made as to whether they were smokers or nonsmokers. Thirty-five of this number, or between nine and ten per cent, gave a definite history of their respiratory allergy being precipitated or aggravated by tobacco smoke. In every case, the smoke was being generated by some other person or persons in the immediate vicinity. Out of these 370 patients, 229 had respiratory allergy. By respiratory allergy is meant hay fever, perennial or seasonal, and bronchial asthma, or asthmatic bronchitis, either or both, with or without accompanying allergic rhinitis.

Out of this entire group of patients, forty-seven, or approximately thirteen per cent, gave positive skin tests to tobacco smoke extract. The same tobacco smoke extract gave negative intracutaneous tests on ten nonallergic controls. There was a correlation of positive history with positive skin tests in nineteen.

From the foregoing, it is apparent that one may become sensitized to tobacco smoke alone, and furthermore that it should be considered an important factor in all respiratory allergy. With this in view, the following studies were carried out in an effort to establish tobacco smoke sensitivity as a distinct allergic entity.

PROCEDURE

STEP I—Blood serum was obtained from an individual giving a positive history of allergy to tobacco, as well as a "4 plus" positive endermal skin reaction to tobacco extract. This serum was diluted with an equal volume of physiological saline, containing four-tenths per cent phenol. With this material, tobacco-sensitized passive transfer sites were made on three nonallergic subjects by introducing 0.10 c.c. intracutaneously. These tobacco-sensitized sites were exhausted with tobacco extract, used in routine skin testing, as follows: 0.05 c.c. of tobacco extract used in routine endermal skin testing was introduced endermally into the transfer sites. This was done every forty-eight hours until the resulting skin reactions became negative, as illustrated in Figure 1. All simultaneous control tests to the same tobacco extract were negative.

STEP II—Approximately 144 hours following the completion of Step I, tobacco-sensitized sites were again made on the same three nonallergic subjects, using tobacco-sensitized serum from the same batch. Attempts were made to exhaust these tobacco-sensitized sites with tobacco smoke

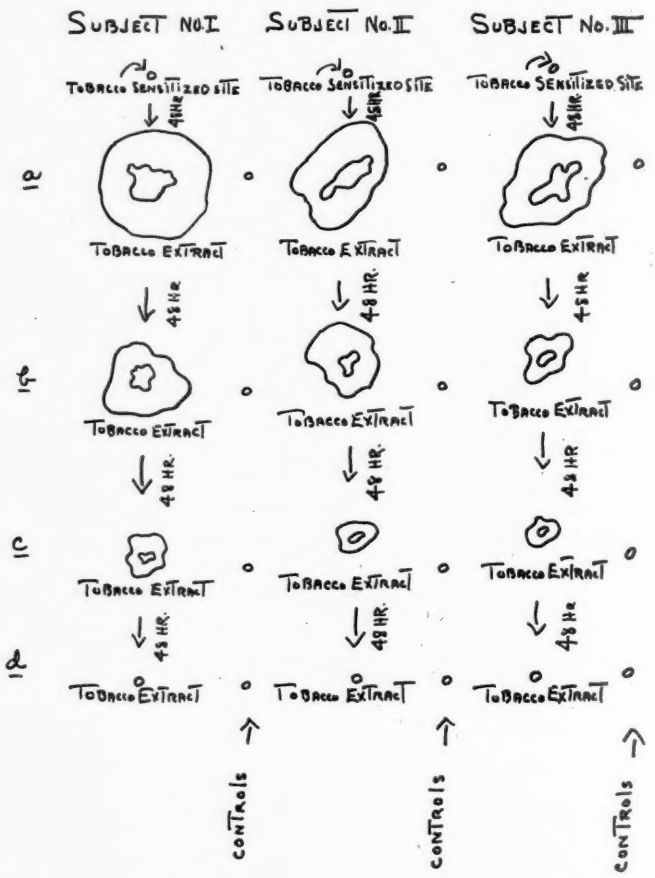

Fig. 1. Tobacco-sensitized passive transfer sites exhausted with tobacco extract.

extract, as follows: 0.05 c.c. of tobacco smoke extract used in routine endermal skin testing was introduced into each of these tobacco-sensitized sites. This was repeated every forty-eight hours until the resulting reactions were negative. Forty-eight hours after the tobacco smoke extract reacted negatively in the three tobacco-sensitized sites, 0.05 c.c. of the tobacco extract used in Step I was introduced into each site. This re-

sulted in positive skin reactions, as illustrated in Figure 2. However, these reactions were reduced in size about 30 to 40 per cent, as compared with the unexhausted reactions in Figure 1. (Compare *a* in Fig. 1 to *d* and *e* in Fig. 2.)

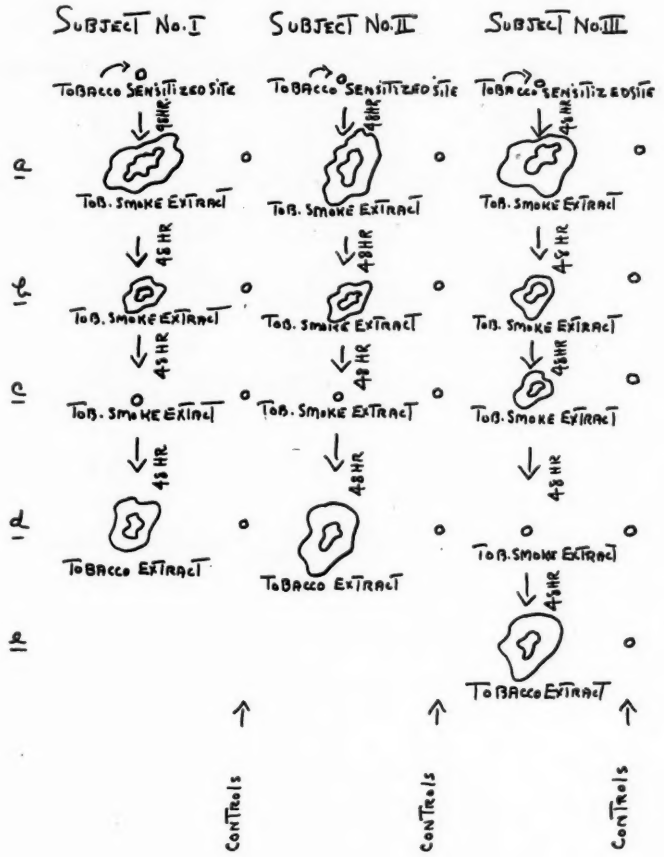

Fig. 2. Tobacco-sensitized passive transfer sites reduced with tobacco smoke extract (compare *d* and *e* in Fig. 2 with *a* in Fig. 1).

STEP III—Approximately two weeks following the completion of Step II, blood serum was obtained from an individual giving a positive history of allergy to tobacco smoke and a "4 plus" positive endermal skin reaction to tobacco smoke extract. This serum was diluted with an equal volume of physiological saline, containing four-tenths per cent phenol. With this material, tobacco smoke-sensitized passive transfer sites were made on three nonallergic subjects by introducing 0.10 c.c. intracutaneously. These

tobacco smoke-sensitized sites were exhausted with tobacco smoke extract used in routine endermal skin testing, as follows: 0.05 c.c. of tobacco smoke extract used in routine skin testing was introduced endermally into the transfer sites. This was done every forty-eight hours until the result-

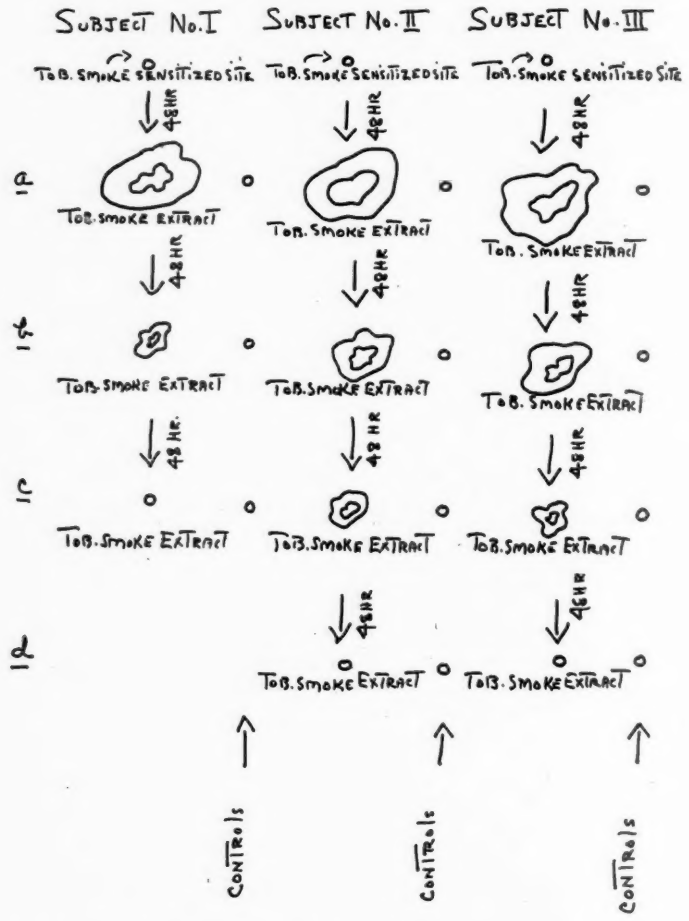

Fig. 3. Tobacco smoke-sensitized passive transfer sites exhausted with tobacco smoke extract.

ing skin reactions became negative, as illustrated in Figure 3. All simultaneous control tests to the same tobacco smoke extract were negative.

STEP IV—Approximately 144 hours following the completion of Step III, tobacco smoke-sensitized sites were again made on the same three nonallergic subjects, using tobacco smoke-sensitized serum from the same

batch. Attempts were made to exhaust these sites with tobacco extract, as follows: 0.05 c.c. of tobacco extract used in routine endermal skin testing was introduced into each of these tobacco smoke-sensitized sites. This was repeated every forty-eight hours, until the resulting reactions were nega-

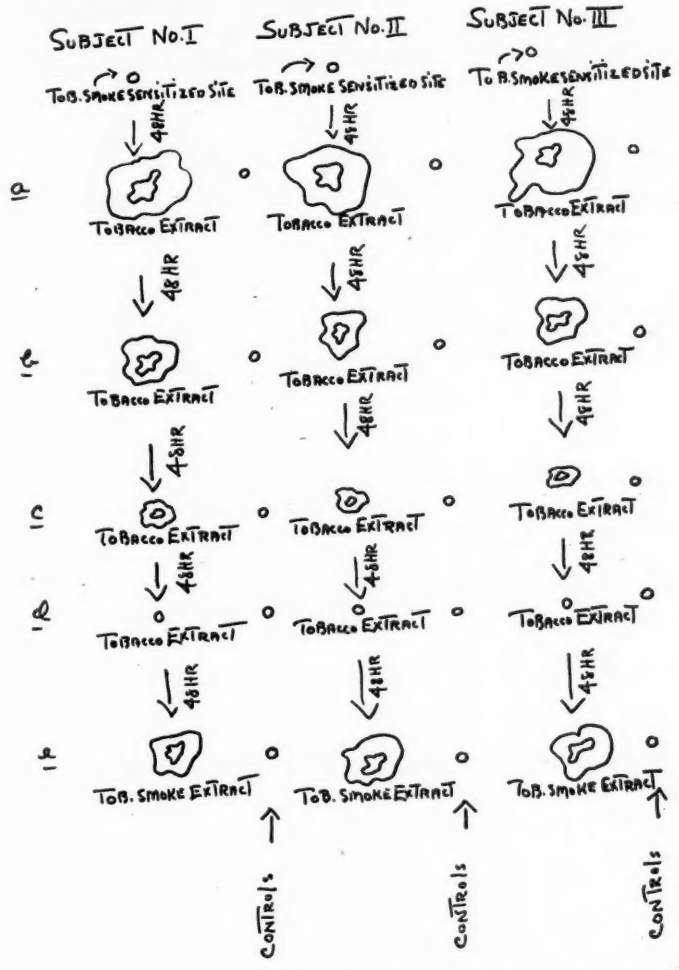

Fig. 4. Tobacco smoke-sensitized passive transfer sites reduced with tobacco extract (compare *e* in Fig. 4 with *a* in Fig. 3).

tive. Forty-eight hours after the tobacco extract reacted negatively in the three tobacco smoke-sensitized sites, 0.05 c.c. of the tobacco smoke extract used in Step III was introduced into each site. This resulted in positive skin reactions, as illustrated in Figure 4. However, these reactions were

reduced about 40 to 50 per cent as compared with the unexhausted reactions in Figure 3. (Compare *a* in Fig. 3 to *e* in Fig. 4.)

SUMMARY

The records of 370 consecutive allergic patients seen in private practice were examined, showing that 9 or 10 per cent gave a definite history of their respiratory allergy being precipitated or aggravated by exposure to tobacco smoke. Approximately 13 per cent of this entire group gave positive skin tests to tobacco smoke extract. This same tobacco smoke extract gave negative intracutaneous tests on ten nonallergic controls.

Passive transfer sites of tobacco-sensitized serum were exhausted with tobacco extract. Passive transfer sites of tobacco-sensitized serum could not be completely exhausted, but were reduced approximately 30 to 40 per cent with tobacco smoke extract.

Passive transfer sites of tobacco smoke-sensitized serum were exhausted with tobacco smoke extract. Passive transfer sites of tobacco smoke-sensitized serum could not be completely exhausted, but were reduced approximately 40 to 50 per cent with tobacco extract.

CONCLUSIONS

1. It is indicated from this study that allergy to tobacco smoke may be a distinct entity, exclusive of allergy to tobacco.
2. It may be further inferred that allergy to tobacco smoke cannot be adequately controlled by hyposensitization with tobacco extract alone.
3. It would probably be well to use both tobacco and tobacco smoke extracts in the course of routine skin testing.

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ATMOSPHERIC POLLEN SURVEYS IN BRAZIL

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UNTIL 1941 a report is not to be found in the literature dealing with pollen counts in Brazil. The first paper on this subject was published in 1942 by Greco, Oliveira Lima and Tupinambá[8], in which they give the results of their investigations on the pollen content of the air in Belo Horizonte, an inland city, about 200 miles northwest of Rio de Janeiro. This year round investigation revealed only one pollen season, that of the grasses, which occurs from mid-May to mid-June. The maximum count was 162 grains of grass pollen per 1.8 square centimeters. Pollens of other plant species were seen on the slides, but in a negligible number and sporadically, without defining a season. This study was carried out under standard conditions, i.e., the slides were exposed daily for twenty-four hours under a protective shelter, at about 8 meters above the ground, from 8 a.m. to 8 a.m., and the count expressed in grains per unit area of 1.8 square centimeters.

After completing this study, Oliveira Lima and the author became interested in knowing the atmospheric pollen situation of other localities of Brazil. They secured the co-operation of several colleagues, also interested in the problem, who were instructed to follow the standard method mentioned here in order to make the slide exposures in their own cities. Boxes holding the slides, especially devised by Oliveira Lima and Greco[12] and coated with glycerin jelly and methyl green, were sent to them. After exposure, the boxes containing the slides were returned to Belo Horizonte where the counting was made by Oliveira Lima and the author. In this way it was possible to cover a large number of localities and obtain data on the pollen content of the air in different sections of Brazil.

In this paper the data secured up to the present writing are summarized.

Daily pollen counts of the air of Rio de Janeiro were made from May, 1941, to July, 1942.[7] In this investigation, it was found also that there was only one season (grass) occurring from mid-May to mid-June. The highest number of pollen grains counted was 58, considerably lower than that of Belo Horizonte. In 1944 Oliveira Lima and co-workers[11] repeated the quantitative pollen studies of the air of Rio de Janeiro. Their findings were found comparable to those of 1941 and 1942.

Oliveira Lima and Greco[13] reported the pollen counts of the atmosphere of Belo Horizonte made during three consecutive years, i.e., 1940, 1941 and 1942. This study showed that, in spite of the variation in the amount of pollen caught from year to year, the season reoccurs at about the same time annually. The 1940 season occurred from the third week of May to the second week of June; in 1941, from May 14 to June 8, and that of 1942 from May 23 to June 15. The highest pollen counts were obtained in 1941; the second highest in 1940; and the lowest in 1942.

Oliveira Lima, Greco and Aguiar[14] made pollen counts of the city of Juiz de Fora (State of Minas Gerais) during the months of May and June. They found a definite grass season extending from May 22 to June 18. Pollen grains of other species were also seen on the slides, but in minute quantity and without seasonal delineation.

A study[16] of the atmospheric pollen content of Campinas (State of São Paulo) shows that this city has a grass season of three weeks' duration beginning in the fourth week of May. The highest count was 100 grains.

The quantitative pollen study of the atmosphere of Varginha (State of Minas Gerais) disclosed a grass season beginning on May 24, reaching a maximum of 100 grains on June 4 and ending June 18.[18] This observation was conducted daily from April to July.

The city of Barbacena (State of Minas Gerais) has a grass season extending from May 28 to June 24.[15] This is the longest season so far observed in Brazil.

Oliveira Lima, Greco and Lula[17] made daily pollen counts of slides exposed in the city of Salvador (State of Baia), from March to August, 1942. This six-month investigation did not show any pollen season. The highest count was 5 granules per unit area of 1.8 square centimeters.

Greco and Oliveira Lima[6] conducted pollen studies in Dores do Indaiá and Abaeté, both in the state of Minas Gerais, during the months of May and June, 1942. They state that both cities have a grass pollen season of about three weeks' duration.

More recently, 1944, Greco and Pereira[9] carried on a pollen study of the atmosphere of Goiania (State of Goiaz). The observation was made daily from May to July, but did not disclose the grass season which has been found in other sections of the county.

According to Greco and Silva Junior[10], in their report of the pollen content of the air of Ribeirão Preto (State of São Paulo), this city shows a grass season of three weeks' duration (May 19 to June 9) with high numbers of pollen grains on the standard slide area (up to 226). Here the observation was made daily from May to August.

According to Greco[1] the cities of Januária and Montes Claros, both in the northern part of Minas Gerais, do not have a grass season in the months of May and June.

Greco and Gabriel Diniz[5] investigated the pollen situation of the atmosphere of Curvelo (State of Minas Gerais). They state that this city presents a grass season of 21 days' duration, but of low pollen concentration. The highest count here was 52 grains.

Greco and França Junior[4] report the result of their study of the pollen content of the air of Serro (State of Minas Gerais) which was done from May to August. They found a grass season which lasted from May 30 to June 19 with a maximum concentration of 108 granules.

Greco and Bastos[3] made daily pollen counts of the air of Santos (State of São Paulo), from June 1 to September 7. This study is not altogether

enlightening because it was begun after the expected starting of the grass season. However, they report that a low grass pollen concentration was found up to June 12. After this date no other pollen was seen on the slides in sufficient number to individualize a season.

Fig. 1. All cities with grass season so far found in Brazil are located within square shown in map.

In 1944 Greco[2] studied the pollen concentration of Belo Horizonte (state capital of Minas Gerais), exposing slides in three different sections of the city: in the business center and in two residential districts at opposite ends of the town. The highest grass pollen count was obtained on the slides exposed in the east district with 400 grains of grass pollen on June 7; the second highest was that of the business center with a maximum of 96; the lowest was observed in the west district with a maximum of 89. The season started on May 21 and ended on June 17, according to the records for the business center of the city. For the residential sections the dates were roughly the same.

Oliveira Lima[11] has been conducting an investigation of the pollen situation of selected cities of the northern and southern parts of Brazil. His report will be of great value to the understanding of the problem.

COMMENT

Though there is a large variety of species of grasses in Brazil, it seems safe to consider the *Melinis minutiflora* (known in Brazil as *Capim gordura* or *Capim melado*) as the chief source of the pollens caught on the

slides during the grass seasons above mentioned, because they coincide with the pollination of this species, and no grass season has been found to occur in sections of the country where *Melinis minutiflora* is not prevalent. Previously it was supposed[8] that *Cynodon dactylon* might be important, but more recently it has been observed that this grass is not as abundant as *M. minutiflora* and its flowering does not coincide with the highest pollen counts.

The only cities so far encountered with a grass season are located withiin a square roughly limited by 18° to 24° lat. couth by 42° to 49° long. west (Fig. 1).

Though definite grass seasons have been disclosed in several cities of the country, the rarity of pollinosis among the Brazilian people is puzzling to the allergists of the country. Cases of asthma, perennial rhinitis, atopic eczema, etc., are almost as frequent there as they are in the United States, but those of hay fever are seldom encountered. The problem of hay fever in Brazil will be reported later.

SUMMARY

Atmospheric pollen counts are reported from the following 16 cities of Brazil, listed by states: *the capital,* Rio de Janeiro; *Minas Gerais,* Belo Horizonte, Juiz de Fora, Varginha, Barbacena, Dores do Indaiá, Abaeté, Januária, Montes Claros, Curvelo, Serro; *São Paulo,* Campinas, Ribeirão Preto, Santos; *Baía,* Salvador; *Goiaz,* Goiania. In all except Januária, Montes Claros, Salvador and Goiania, was found a well-defined grass hay-fever season extending from mid May to mid June. This is caused principally by the pollen of *Melinis minutiflora (Capim gordura* or *C. melando)* and to a lesser extent that of *Cynodon dactylon.*

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EXPERIMENTAL APPROACH TO ORAL TREATMENT OF FOOD ALLERGY

III. Oral De-allergization with Food Propeptans of Orally Allergized Animals

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THE great majority of individuals who present any kind of manifestation of food allergy have acquired their allergy by the enteral route. Moreover, the various symptoms of an underlying food hypersensitiveness are—almost exclusively—elicited by ingestion of the food in question. For many years, the senior author[8] has pointed to the fact that the oral administration of food digests—the so-called food propeptans*—can at first temporarily inhibit a given food allergy, and then ultimately cure the condition completely.

The present paper is concerned with an investigation of this question along lines of animal experimentation.

Animals were allergized *orally* by means of food extracts; the allergic symptoms were elicited by *oral* administration of food extracts, and these very symptoms were inhibited by means of food propeptans, given *orally*. Similar experimental work with propeptans has been reported by Hamamoto.[4] These results would seem to constitute experimental confirmation of the therapeutic significance of specific food digests.

It is relatively easy to achieve experimental allergization by way of the mouth. Thus, guinea pigs can be allergized by oral administration of substances to which they are not accustomed—e.g. horse serum (Rosenau and Anderson, Aurichio, Hettwer and Kriz), milk (Vaughan), egg (La Roche, Richet and Saint Girons), and so on.

However, this does not occur in anything like the high incidence of shock that follows intravenous injection of the antigen. Thus, as Ratner[7] has reported, three out of forty-four orally allergized animals presented violent anaphylactic reaction to 5 c.c. of skimmed milk by mouth, while eleven of this series responded with moderate anaphylaxis to the same dose; and the remaining thirty animals presented little, if any, reaction. On the other hand, 50 per cent responded to milk, injected intravenously, with anaphylactic shock. Also, Hamamoto[3] found that only few of his

From the Department of Allergy, Jewish Hospital. Expenses for this work were defrayed in part by a grant from the Allergy Research Foundation, Inc., Philadelphia, Pennsylvania.

Sequel to "Experimental Approach to Oral Treatment of Food Allergy. II. Immunologic Properties of Food Propeptans." Ann. Allergy, 3:172, (May-June) 1945.

*Food propeptans are food digests derived from the individual foods through prolonged digestion with hydrochloric acid and pepsin, followed by some slight additional digestion with trypsin. Thus, these preparations contain all the protein cleavage products, chiefly proteoses but also peptones, sub-peptones, simple peptids and amino acids but not any native proteins (Urbach, Jaggard and Crisman.[11]) However, for reasons stated elsewhere in this paper, glycyrrhiza is added to the propeptans intended for therapeutic use. This saponin contains 1.4 per cent protein nitrogen. Pure food propeptans for analytic or experimental purposes will be supplied by Dalare Associates, 2300 Locust Street, Philadelphia 3, Pa., on request.

TABLE I. EFFECT OF ADDITION OF GLYCYRRHIZA ON DEGREE OF ENTERAL ALLERGIZATION OF GUINEA PIGS

Enteral Allergization*	Interval	Concentration of Allergen†	Clinical Manifestations
Egg white alone		1:10,000	Fatal anaphylactic shock
	2 weeks after last previous' ingestion	1:100,000	Slight pruritus
		1:10,000,000	No symptoms
Egg white + 0.1 gm. of glycyrrhiza each day		1:100,000	Fatal shock
		1:10,000,000	Fatal shock

*Feeding of 0.1 gm. of egg white for seven days.
†Dilution of egg white necessary to elicit anaphylactic shock in 1 c.c. doses, intravenously.

experimental animals, which had been orally allergized to milk, died from fatal shock when milk feeding was repeated after a two weeks' interval.

In order to achieve oral allergization in a higher percentage of instances, as reported above, irritation of the gastro-intestinal tract, e.g. by means of alcohol, may be tried (Hajos[2]). Furthermore, the degree of resorption can be greatly increased by removing the protective layers of mucus covering the mucous lining of the small intestine, e.g. by means of ox gall. Arloing, Langeron and Spassitch[1] claim that in this manner, they have succeeded in allergizing guinea pigs to antipyrine, quinine and olive oil. However, since animals do not readily tolerate ox gall, Urbach[9] augmented the allergizing properties of food antigens by adding the saponin glycyrrhiza which serves to increase resorption by dissolving the mucus of the small intestine (Table I). With the use of glycyrrhiza he even succeeded in allergizing guinea pigs orally to food digests.

ORIGINAL EXPERIMENTS

Fifty virgin guinea pigs, weighing approximately 250 grams, were allergized by oral administration of 2.5 c.c. of liquid egg white+0.2 grams of glycyrrhiza for seven consecutive days. And, as an alternative, another fifty animals were given 1 c.c. of 25 per cent alcohol solution followed immediately by 2.5 c.c. of liquid egg white.

These *orally* sensitized animals were highly sensitive three weeks after the last feeding, as shown by the fact that they responded with fatal anaphylactic shock to *intravenous* injection of 0.25 c.c. of 0.1 per cent liquid egg white.

Experiment 1

Guinea pig 720, sensitized to egg white by oral administration of 1.0 c.c. of 25 per cent alcohol solution followed immediately by 2.5 c.c. of liquid egg white daily for seven days.

Three weeks later the following procedure was carried out:

Treatment: None.

Shock Dose: Intravenous injection of 0.25 c.c. of 0.1 per cent liquid egg white.

Symptoms: Immediately fatal anaphylactic shock.

Schultz-Dale Test: Negative.

Lung Perfusion Test: Maximally positive

Similar but, in general, less dramatic reactions are caused if the shock dose is given by mouth. Thus, when an animal which had been sensitized orally was given the shock dose (7.5 c.c. of liquid egg white) by mouth,

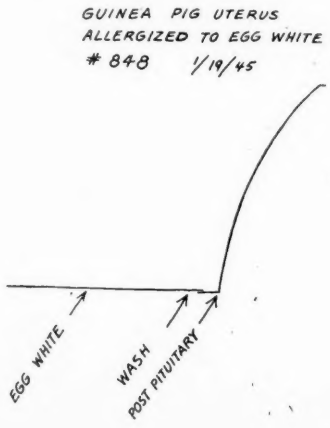

Fig. 1. Schultz-Dale test performed upon the uterus of guinea pig No. 848, allergized to egg white by the oral route, and killed two hours after the oral administration of a shock dose of egg white. There was no reaction upon the addition of egg white, indicating the absence of antibodies for native (unaltered) egg white. A final addition of posterior pituitary extract was made as a check upon the sensitivity of the uterus.

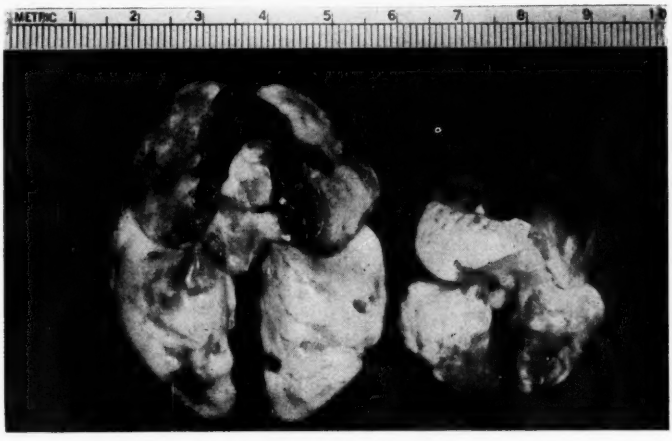

Fig. 2. Lung perfusion test performed upon the lung of guinea pig No. 848, allergized to egg white by the oral route and killed two hours after the oral administration of a shock dose of egg white. The lung *(left)* showed maximal inflation, indicating that the lung tissue is highly allergized. A control lung of a nonallergized animal of the same weight *(right)* showed a negative reaction in the lung perfusion test.

it presented, after five minutes or so, mild but definite allergic manifestations as evidenced by bristling, coughing and gasping respiration. These symptoms disappeared within half an hour. In two instances the guinea

pigs died in acute anaphylactic shock. Again the Schultz-Dale test was negative and the lung perfusion test brought on maximal inflation of the lung.

Experiment 2

Guinea pig No. 848, sensitized to egg white by oral administration of 1.0 c.c. of 25 per cent alcohol solution followed immediately by 2.5 c.c. of liquid egg white daily for seven days.

Three weeks later the following procedure was carried out:

Treatment: None.

Shock Dose: Oral administration of 7.5 c.c. of liquid egg white.

Symptoms: Approximately five minutes after the shock dose the animal bristled, coughed and gasped deeply. The guinea pig recovered in half an hour.

Animal killed two hours after the oral shock dose.

Schultz-Dale Test: Negative (Fig. 1).

Lung Perfusion Test: Maximally positive (Fig. 2).

In contradistinction to *orally* sensitized animals, *parenterally* allergized guinea pigs will consistently exhibit both positive Schultz-Dale reactions and positive lung perfusion tests (Urbach, Jaggard and Crisman[12]).

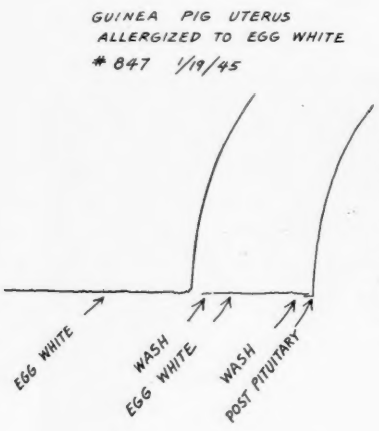

Fig. 3. Schultz-Dale test performed upon the uterus of a guinea pig, No. 847, allergized to egg white parenterally and killed two hours after the oral administration of a shock dose of egg white. There was a violent reaction following the addition of egg white, indicating the presence of considerable quantities of antibodies for egg white. No reaction followed a second addition of egg white, proving that the preceding one was specific. A final addition of post-pituitary extract was made as a check upon the sensitivity of the uterus.

Experiment 3

Guinea pig No. 847, allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline.

Three weeks later the following procedure was instituted.

Treatment: None.

Shock Dose: Oral administration of 7.5 c.c. of liquid egg white.

Reaction: Bristling and coughing in about five minutes followed by severe gasping respiration for about one hour, after which the guinea pig recovered.

Animal killed two hours after the shock dose.

Lung Perfusion Test: Positive (Fig. 3).

Schultz-Dale Test: Positive (Fig. 4).

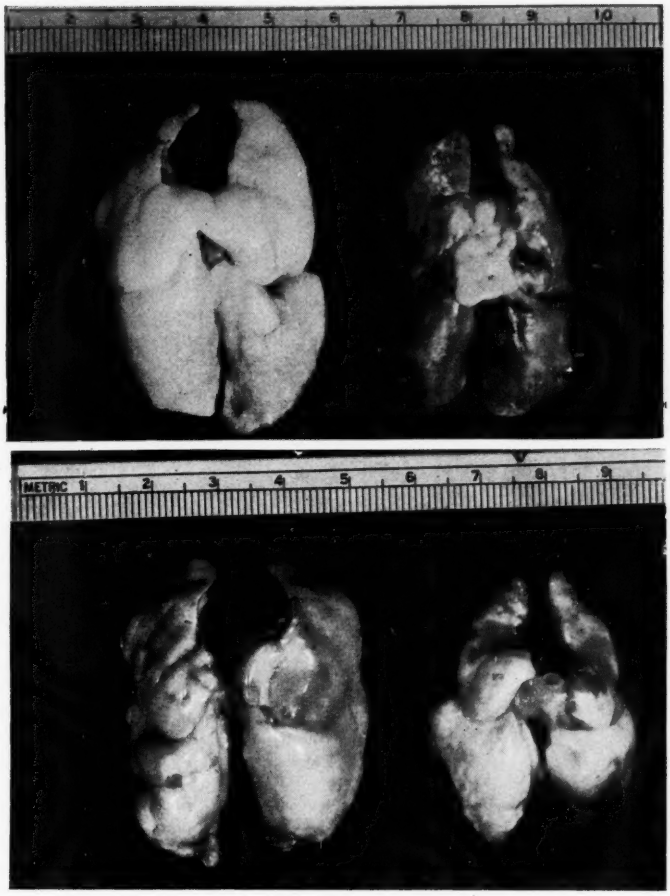

Fig. 4 *(above)*
Fig. 5 *(below)*

Figs. 4, 5, 6 and 7. Lung perfusion test of animals in different states of de-allergization.

Guinea pigs are allergized to egg white by daily oral administration for seven consecutive days.

Three weeks following oral administration of egg white, guinea pig No. 847 (Fig. 4) exhibited a maximal positive reaction to egg white in the lung perfusion test. Guinea pig No. 775 (Fig. 5), treated with a series of *intravenous* injections of egg propeptan in increasing doses, received an oral shock dose of egg white. The lung perfusion test was less marked but definitely positive. Guinea pig No. 724 (Fig. 6) received one *oral* treatment with egg propeptan, followed by an oral shock dose of egg white. The lung was slightly but definitely positive. Guinea pig No. 749 (Fig. 7) received *oral* treatment with egg propeptan on *four consecutive days* always followed by an oral shock dose of egg white. Lung perfusion test was persistently negative.

Control lungs of nonallergized animals of same weight *(right)* show negative reactions in lung perfusion tests.

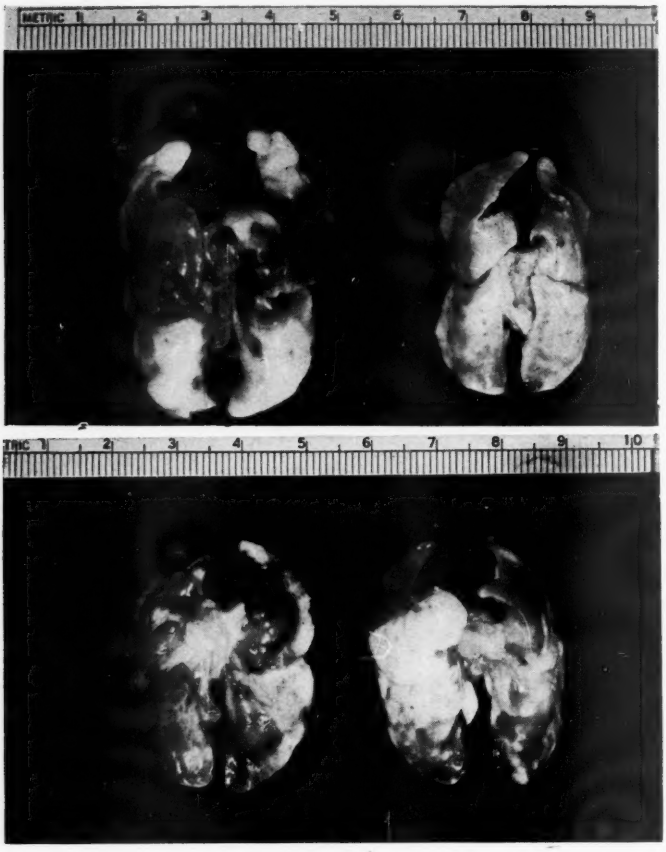

Fig. 6 *(above)*
Fig. 7. *(below)*

How can one explain the most unusual fact that the uterus of animals, highly sensitized by the oral route, do not react to the addition of the specific antigen while the lung in the Manwaring-Kusama[6] test presents a maximal emphysema and animals of this series die instantaneously when the very same antigen is intravenously injected in very small amounts? There is not the slightest doubt that the Schultz-Dale test constitutes the most reliable and sensitive method for determination of sensitization of laboratory animals on one hand, and for the specificity of antigens, on the other. Yet, the high specificity of the Schultz-Dale is precisely the flaw which makes this procedure less useful for certain biologic and immunologic purposes than the anaphylactic or the skeptophylactic experi-

ments performed in living animals (Urbach and Wolfram[13]). This is because the Schultz-Dale method is so extremely specific that a positive reaction can be evoked only if the antigens used in the sensitization of the animal and in its reinjection are absolutely chemically identical. However, when antigens are immunologically related as to type-specificity but are not chemically identical they cannot produce a uterine reaction. The immunologic relationship which exists between a native protein and its digestion products (proteoses and peptones) and for which the term type-specificity is used, cannot be demonstrated by means of the Schultz-Dale test, but can readily be shown by less specific biologic methods such as the lung perfusion test and the anaphylactic experiment on the living animal.

When egg white is given orally, it is subjected to degradation both in the stomach and in the small intestine. The degradation products, especially the proteoses, are partly resorbed as such if the gastro-intestinal tract has been previously irritated by alcohol, or its resorptive capacity increased by glycyrrhiza, instilled in the stomach. This means that animals so prepared are sensitized not to native egg white but to proteoses of egg white. The reason that addition of native egg white to the sensitized uterus evokes no reaction is that the uterine muscle is unable to respond to the proteoses which, while they are immunologically related to egg white, are, however, chemically not identical with it. On the other hand, the lung perfusion test and the anaphylactic experiment are less specific and will react therefore to type-specific antigens (proteoses and the protein from which it is derived) although they are not chemically identical.

The same negative results are obtained as in orally sensitized animals, when one attempts to perform a Schultz-Dale test with egg propeptan on the uterus of an animal *parenterally* sensitized to egg white, or with egg white on the uterus of an animal *parenterally* sensitized to egg propeptan. W. Jadassohn and Schaaf[5] failed to take these principles into account when they disputed the type-specificity of propeptans, because these protein degradation products are unable to produce a positive Schultz-Dale test in animals sensitized to the native protein.

Our next problem was to determine how to prevent anaphylactic manifestations from making their appearance, following oral administration of a shock dose.

We could demonstrate that when orally allergized animals are given gradually increasing doses of food propeptans by intravenous injections at ten-minute intervals, the oral shock dose fails to elicit any clinical symptoms. When the animal is killed, two hours later, the Schultz-Dale test is found to be negative. The lung, however, is slightly but definitely inflated, a finding which indicates that the preparatory intravenous administration of propeptans has not satiated all of the antibodies.

Experiment 4

Guinea Pig No. 775 allergized to egg white orally. By mouth, every day for seven days: 1.0 c.c. of 25 per cent alcohol solution, followed immediately by 2.5 grams of egg white.

Three weeks later the following treatment was instituted.

Treatment: Intravenous injections of egg propeptan at ten-minute intervals.

Injection 1—Egg Digest representing 1.0 mgs. of Soluble Nitrogen—No reaction
Injection 2—Egg Digest representing 2.5 mgs. of Soluble Nitrogen—No reaction
Injection 3—Egg Digest representing 5.0 mgs. of Soluble Nitrogen—No reaction
Injection 4—Egg Digest representing 10.0 mgs. of Soluble Nitrogen—Slight bristling
Injection 5—Egg Digest representing 20.0 mgs. of Soluble Nitrogen—Bristling

After fifteen minutes—

Shock Dose: By mouth 7.5 grams of egg white.

Symptoms: No clinical symptoms.

Animal killed two hours after the oral shock dose.

Schultz-Dale Test: Negative.

Lung Perfusion Test: Slightly but definitely positive (Fig. 5).

Very similar results are obtained when the allergized animal is given only one oral dose of egg propeptan representing 20 mg. of soluble nitrogen + 0.2 grams of glycyrrhiza, dissolved in 3 c.c. of water, and then the shock dose by mouth after a sixty-six-hour interval. Here, too, the animal presents no clinical symptoms, but the lung is again moderately inflated.

Experiment 5

Guinea Pig No. 724, allergized to egg white orally. By mouth, every day for seven days: 1.0 c.c. of 25 per cent alcohol followed immediately by 2.5 grams of egg white.

Three weeks later the following treatment was instituted:

Treatment: By mouth, egg digest representing 20 mgs. of soluble nitrogen + 0.2 grams of glycyrrhiza + 3.0 c.c. of water.

Sixty-six hours later

Oral Shock Dose: By mouth, 7.5 grams of egg white.

Symptoms: Animal slightly restless, but otherwise no apparent change. Animal killed two hours after the oral shock dose.

Schultz-Dale Test: Negative.

Lung Perfusion Test: Slightly but definitely positive (Fig. 6).

Yet, when the oral shock dose is administered at some other time—for example, after an interval of twelve, twenty-four and forty-eight hours, there is pronounced inflation of the lung. The reasons for the necessity of waiting about sixty-six hours are not clear. However, our experience has shown that in guinea pigs this interval must elapse in order to protect the animal against the oral shock doses. This is, of course, quite different from the interval in human beings where three quarters of an hour was found to be the optional time.

However, when the animals are given the propeptan orally on four consecutive days followed each time by the oral shock dose they will be entirely free from clinical symptoms on the second or third day. Lung perfusion tests performed on the fourth day will reveal no inflation of the lung whatsoever, a clear indication that the antibodies in the primary shock tissue (e.g. the lung) have been completely satiated.

Experiment 6

Guinea pig No. 749, allergized to egg white orally. By mouth, every day for seven days: 1 c.c. of 25 per cent alcohol solution, followed immediately by 2.5 grams of egg white. Three weeks later the following treatment was instituted:

Treatment: Daily schedule for four consecutive days.
5:00 P.M. Animal fed.
6:30 P.M. Food and bedding removed; animal kept in bare cage over night.
8:00 A.M. By mouth, egg propeptan representing 20 mgs. of soluble nitrogen + 0.2 grams of glycyrrhiza + 3.0 c.c. of water.
8:45 A.M. Shock dose, by mouth, 7.5 grams of egg white.
Symptoms: Slight restlessness and shaking of head after first administration of egg white. No clinical symptoms following the other oral doses of egg white.
Animal killed on the fourth day, two hours after the last feeding of egg white.
Schultz-Dale Test: Negative.
Lung Perfusion Test: Negative (Fig. 7).

However, the interval between the administration of the propeptan and of the oral shock dose must be no less than thirty minutes and no more than nine hours, otherwise the lung test will reveal marked inflation. In order to explain this rather puzzling finding we refer the reader to the theory of oral de-allergization.[10] This concept assumes that this form of de-allergization is accomplished by microshocks. The time of thirty minutes is probably necessary for the propeptan to neutralize (satiate) the antibodies of the lung of the allergized animal while after nine hours this neutralization is broken up by the formation of newly formed antibodies in the primary shock organ. In addition, it is necessary to allow two hours to elapse between administration of the food antigen and performance of the uterus and lung tests.

When another food digest (e.g. chicken propeptan) was given instead of the egg propeptan, we observed pronounced clinical anaphylactic manifestations and maximal inflation of the lung in the lung perfusion test. Thus, the type-specificity of the propeptans was demonstrated once again.[12]

SUMMARY

The conditions which lead to food allergy in human beings were reproduced in animal experiments. Animals were allergized *orally* by means of food proteins; allergic manifestations were elicited by *oral* administration of the very same food proteins, and these symptoms were inhibited by means of *orally* administered food digests (food propeptans).

By irritating the gastro-intestinal tract by means of alcohol, or by increasing the resorptive capacity of the intestinal mucosa by means of glycyrrhiza, it is possible to allergize guinea pigs orally to native food protein. After an interval of three weeks, food of the same type, administered orally, can evoke clinical anaphylactic manifestations and maximal emphysema in the lung perfusion test.

The observation was made that animals orally sensitized to food proteins to such an extent that they died instantaneously on intravenous injection of a very small amount of antigen invariably showed a negative

Schultz-Dale reaction, while the lung perfusion test was always positive. On the other hand, guinea pigs parenterally sensitized to a similar degree consistently exhibited both positive Schultz-Dale and lung perfusion test to the same oral shock doses. The mechanism underlying this difference is discussed.

In oral treatment food propeptans are effective only when followed after a certain interval of time by the corresponding food allergen *by mouth.* They will fully inhibit the clinical and characteristic pathological allergic manifestations, provided this procedure is continued for several consecutive days. Moreover, they will neutralize the antibodies in the primary shock organ, the lung, as evidenced by negative lung perfusion test.

The action of the propeptans is based on the principle of skeptophylaxis (anti-anaphylaxis) and leads first to temporary and later to lasting de-allergization.

It is highly probable that, in every-day life, oral de-allergization in human beings is brought about mainly by physiologically formed degradation products of food proteins digested in the gastro-intestinal tract, such as proteoses and peptones.

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SENSITIVITY TO THE ORAL ADMINISTRATION OF CASTOR OIL

MAJOR PHILIP BLANK, MC

A SEARCH through the literature has failed to reveal any report of sensitivity to the oral administration of castor oil, although there is mention of many instances of contact sensitivity to castor oil and inhalant sensitivity to castor bean dust. A case of dermatitis medicamentosa due to the oral administration of castor oil was seen at the Station Hospital, Fort Eustis, Virginia.

CASE HISTORY

A well-developed, white, male soldier, aged twenty-three, with no history of major or minor allergic episodes but with a history of fall type hay fever in a maternal uncle, received an ounce of castor oil in an outpatient infirmary. The patient had received no castor oil since childhood and could remember no untoward reaction at that time. Within twenty minutes after the administration of the drug, it was reported that the patient began having marked generalized abdominal cramps and diarrhea. Within two hours, the patient's tongue and fauces were reddened and slightly edematous. He developed a marked erythematous flush about the face. The patient was admitted to the hospital as a scarlet fever suspect about an hour later. On admission he presented a scarlatiniform rash over his face, neck and shoulders, moderate edema of both eyelids, lips and ears, a moderately severe stomatitis with reddening and slight edema of the fauces, and a slight generalized tenderness over his abdomen. The patient complained of a flushed, feverish feeling about his face and neck, especially of his ears and mouth, and of generalized abdominal cramps and some tenesmus. He was apprehensive and complained of marked generalized weakness. The admission temperature was 99.2 degrees F. by mouth and the pulse rate 100. Within three hours after admission, the patient developed a mild conjunctivitis, rhinorrhea of a clear watery fluid, a punctate vesicular papular rash over his neck and shoulders and a generalized extension of the erythema which resembled a scarlatiniform rash. Twenty-four hours after admission, the rhinorrhea and the conjunctivitis had subsided, the edema of the lips, ears and eyelids had regressed almost completely and the tiny vesicles were drying up. In forty-eight hours, a fine powdery desquamation began over his neck and shoulders and extended gradually over the entire body. The patient was apparently completely recovered in four days. The diagnosis of dermatitis medicamentosa was made and castor oil was suspected as the offending agent.

After allowing a three-day rest, the patient was given a clinical test with 4 c.c. of castor oil orally. The clinical picture seen previously was reduplicated exactly but to a slightly less degree. Desquamation again occurred. After three weeks, a third clinical test was given with 1 c.c. of castor oil. The patient developed erythema but without vesiculation, mild edema of the eyelids, mild cramping abdominal pains but no diarrhea and slight rhinorrhea. No desquamation developed.

The laboratory reported a leukocyte count of 5,800 cells and an eosinophilia of 6 per cent. Scratch-patch test showed only a slight reaction to castor oil. Patch test with castor oil was negative.

It is felt that the diagnosis of dermatitis medicamentosa due to the oral administration of castor oil was justified, and was sustained by repeating the clinical syndrome with two clinical trials of oral administration of castor oil.

This case is thought to be the first reported case of sensitivity to the oral administration of castor oil.

Major Blank is a Fellow of the American College of Allergists.

Editorial

GRADUATE INSTRUCTIONAL COURSE

Pursuant to the College's policy of pioneering intensive graduate continuation courses in allergy in centrally located areas easily accessible from all parts of the country and Canada, its third course will be held at Thorne Hall, Northwestern University, Chicago, from Monday morning, November 5 to Saturday noon, November 10.†

Owing to its proximity to the Northwestern University Medical School, the Pearson Hotel, 190 East Pearson Street, is suggested for both students and instructors. In case the reservations there are filled, the applicants can be accommodated at either the Seneca Hotel, the Knickerbocker Hotel or the Drake. An informal dinner will be held Monday evening, November 5, at the Pearson Hotel so that the registrants may become better acquainted. The members of the Chicago Allergy Society have been invited to attend. Dr. William H. Welker, Head of the Department of Biological Chemistry, Director of Research of the Allergy Unit, and Dean of the University of Illinois College of Medicine, will speak at the dinner on "Antigenicity of Proteins in Relation to Allergy."

The most outstanding leaders in their respective fields are enthusiastic in their participation when making this one of the most outstanding graduate courses in allergy ever to be presented in this country. No effort is being spared to satisfy the registrants whether they are advanced students of allergy wishing to refresh their knowledge of the subject, those training for specialization in allergy, or the non-specialist seeking graduate training.

Seventy-two registrants attended the course conducted by the College in St. Louis last November. Of these members and non-members, twelve were in active service. Available outlines of the November courses (printed on sheets which fit a standard ring book) are still in demand. The Educational Committee urges that as many members of the College as possible, as well as candidates for Active and Associate Fellowships and non-members, avail themselves of this opportunity and register early, since registration of those outside the Chicago area may be limited by the Office of Defense Transportation. Hotel reservations should be made immediately.

All men in the Service at the time of their registration will be admitted without charge, otherwise the regular fee of one hundred dollars will be required. All registrants will receive outlines of the courses as well as the revised printed Manual of Allergy Laboratory and Diagnostic Procedures.

All those wishing to register for this course will please communicate with the Secretary, American College of Allergists, 401 La Salle Medical Building, Minneapolis, Minnesota.

†See editorial in the May-June, 1945, issue of the ANNALS—Page 210.

RESEARCH ON BLOOD GROUPS

Living tissue seems to have the general ability of reacting on the introduction of foreign matter with the production of proteins that can combine specifically with the matter introduced. It is well to keep aware of this fact because for a real understanding of immunological phenomena, it is essential to realize that antibody formation is a fundamental biological function without evident predetermined direction of action. Our mental makeup experiences the need of a purpose in all phenomena of life. In satisfying this need and also under the pressure of the practical needs of medicine, we have become used to split the biological phenomena connected with antibody formation into two compartments: One, we call immunology, and we tuck away in this compartment those antibody effects which seem to fulfill a useful purpose, particularly those cases where antibody neutralizes or contributes to destroy a microbial invader or its toxic products. The other, we call allergy, and into this compartment we sort out antibody activities which present a nuisance and sometimes a danger to life and happiness of man and his four-legged co-sufferers. The only *apparent* purpose of these phenomena in the established order of things is to provide for an interesting specialty in the profession of medicine.

There are antibody-antigen reactions that do not fit in either compartment. Some of them we produce experimentally and they are particularly favorable objects for the study of basic problems of antibody action. Others are offered to us by nature and a closer acquaintance with these is very much worth while just because they shake our belief in the purposefulness of this peculiar system of physiological activity. Among these, the study of blood-specificity is of particular interest (*and* of great practical importance).

Our readers will have found in the preceding issue of this journal, a review by A. S. Wiener concerning one of the most recent developments in this field, namely, the Rh factors. The author of our article has presented a synopsis of the whole field of research on blood-specificity in a book* which makes very good reading indeed, and which we would wish to see in the hands of many of our colleagues. This book unfolds the story of over 40 years of patient unraveling of one puzzling phenomena after the other. The discoveries of the various types of blood-specificity—the basic A-B-O system, the factors M, N and P, and the youngest member of the family, the Rh factors—have deeply influenced our thinking about the problems connected with individuality and heredity. The field of blood group research has presented particularly favorable conditions for the application of exact statistical and genetic analysis, and these methods have been employed with remarkable suc-

*Wiener, A. S.: Blood Groups and Transfusions. Third edition, XIX, 438 pages, 69 figures, 106 tables. Springfield, Ill.: C. C. Thomas, 1943.

cess. Clinical allergy could greatly profit by adopting similar points of view and methods of research.

The case of blood-group research demonstrates what can be done when the right man gets a real chance to go to the roots of a great problem. The result was a golden harvest of theoretical and practical results. Clinical allergy has accumulated an enormous and sometimes confusing mount of observational material. What is needed is the strengthening of the foundation on which our house is built. This is only possible by fundamental research carried on without regard to immediate application. The future development of our field makes it imperative to invest in sustained curiosity, that is, to foster working conditions conducive to long-range and consistent investigational effort. The policy of the College in this respect is very definite. It has found its first expression in collecting means for research fellowships, and in efforts to bring the clinical allergist in contact with related fields and with science in general.

A. J. Weil

THE MANUAL OF ALLERGY LABORATORY AND DIAGNOSTIC PROCEDURES*

This practical, new, revised Manual, compiled by members of the College, is ready for mailing. The supply of the first mimeographed edition, issued at the St. Louis instructional course last fall, having soon become exhausted, a second enlarged, printed, loose-leaf edition (8½ x 11), permitting supplemental or revised procedures, has been published. It is bound in a standard ring book of exceptional, durable qualiity. The Manual includes detailed methods of making allergenic extracts of all kinds and their standardization. The table of contents is a complete guide to the material included.

Laboratory procedures for preparing allergenic extracts and their application, various methods of testing and the treatment of allergies, the technique of pollen surveys and miscellaneous information valuable to students of allergy are briefly described therein. This condensed information is based upon knowledge gleaned from authoritative textbooks and other published articles on the subject as well as years of personal experience of the collaborators, with the hope that it will save valuable time. For detailed description, however, the reader is referred to the many excellent texts on the subject.

Published in loose-leaf form, it readily enables supplementary information from time to time, as occasion arises, in order to present a concise, up-to-date Manual.

*See page 331 of this issue for a review of the Manual.

Progress in Allergy

ALLERGIC SKIN DISEASES

Eczema—Urticaria—Drug Eruptions
A Critical Review of Recent Literature

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Marshfield, Wisconsin

ECZEMA—ALLERGIC DERMATITIS

A definition of terms was presented in last year's review.[38] It must suffice to repeat that eczema and allergic dermatitis are used practically as synonyms. The term eczema is used morphologically to denote a superficial inflammation of the skin with or without vesiculation, more or less sharply outlined, acute, subacute or chronic, usually itching at one time or other, and in many instances recurring. Eczema will be reviewed under the following four headings: (1) Atopic Dermatitis, (2) Contact Dermatitis (Epidermitis), (3) Microbic (mycotic, bacterial, parasitic) Eczema, and (4) Other Forms of Eczema.

ATOPIC DERMATITIS

The distinction between atopic dermatitis (neurodermitis) and contact type dermatitis (epidermitis) is challenged by Cooke.[19] He claims that these two forms of eczema are immunologically identical and suggests that the terms atopic dermatitis and neurodermatitis should be eliminated. Cooke maintains that atopic dermatitis (also in older children and adults) has no known points in common with hay fever and other wheal-producing allergies. This claim is partially based on the fact that the result of the scratch or intradermal test is a wheal and not an eczema. "With the tests we should seek to duplicate (reproduce) the essential characteristics of the clinical reaction." (Cooke's requirement, if taken literally, would also challenge the value of a scratch test as a diagnostic aid in hay fever or asthma.) Cooke has never observed an exacerbation of eczema from the ingestion of the foodstuff which gave an immediate wheal reaction. He too stresses the frequent association of eczema and wheal-reacting allergies in the same infant, but cannot explain it with his theory.

Those who distinguish the atopic form from etiologically different forms of the so-called infantile eczema, are aware that a positive intradermal or scratch test usually (in infants as well as adults with atopic dermatitis) produces a whealing reaction and only rarely a delayed eczema-like reaction. On the other side, most of these patients do *not* present clinical signs of urticaria. These facts by themselves are no proof or even an indication that the two phenomena (whealing test and atopic eczema) are not related. I may mention an anology in sunlight allergy.[37] There are cases of light dermatitis (prurigo estivalis as well as hydroa vacciniformis) that clinically present only symptoms of an eczema or a papular or vesicular eruption and no wheals. The skin tests with ultraviolet light performed on normal skin in many of these cases produce only an immediate whealing reaction. Urticarial ultraviolet reactions are so rare that there cannot be any doubt as to their etiological relation with the eczema- or prurigo-like type of eruption from which these patients suffer.

*From the Marshfield Clinic.

The reader will find some of the facts and reasons that urge a separation of atopic dermatitis and contact type dermatitis in last year's review[38]; the question of their interrelation also has been discussed. The difference of the two forms may not be as fundamental as generally thought. The possibility of epidermal sensitization in atopic dermatitis must be admitted. MacCardle, Engman and Engman[83] believe that the development of a lesion in neurodermatitis (atopic dermatitis) is located in the spinous cells of the epithelium. On the other hand, the occurrence of dermal sensitivity in contact type dermatitis is a fact, shown especially in epidermitis due to sensitivity to nickel or chromates. One may agree with Cooke[19] that the paucity of our knowledge has led to confusion. Some of the present concepts need revision. Cooke's arguments will stimulate discussion. But at this juncture it does not seem justified to throw overboard the distinction between atopic skin sensitivity and contact type sensitivity and their manifestations—a distinction which constitutes perhaps the greatest practical advance of modern dermatology.

A histologic attempt at differentiating various forms of eczematoid dermatoses is presented by Sachs, Miller and Gray.[112] Contact dermatitis (epidermitis) is characterized by small vesicles, frequently in the upper part of the epidermis, little or no acanthosis (thickening of the epithelium), and a mild superficial inflammatory reaction. In contradistinction, atopic dermatitis has a nonedematous regular acanthosis, thickening of the walls of the small arteries and a focal cellular reaction. The pathological features of nummular eczema appear to be chiefly those of neurodermatitis (atopic dermatitis) plus an epidermic vesicle. In addition to these three forms of eczema the authors describe a fourth one which they call eczema (without any further specification). It differs from the other three by an extensive cutis reaction, with special involvement of the capillaries. This study confirms the principal histologic differences between clear-cut cases of contact dermatitis and atopic dermatitis. However, morphological histopathology offers little help for investigation of the numerous atypical or combination of forms of eczema.

Histochemical studies may be more promising. It has been shown by MacCardle, Engman and Engman[83] that magnesium deficiency is found in active atopic skin lesions. Sullivan and Evans[129] compared atopic dermatitis with experimental magnesium deficiency in rats. The authors conclude that it was not possible to establish the claim that these two conditions are identical or similar diseases. The clinical symptoms and the microscopic changes are dissimilar in the two conditions. Furthermore, in the experimental disease of the rat there is a decrease or absence of magnesium in the blood but not in the skin, whereas in atopic dermatitis of humans there is a decrease or absence of magnesium in the skin but no change in the blood level.

Atopic Dermatitis by Contact.—It is important to distinguish between "atopic dermatitis by contact" and the so-called "contact dermatitis." The essential shock organ in atopic dermatitis is the vascular-connective tissue layer, in contact dermatitis (epidermitis) the epidermis (epithelium). The route of the allergen is immaterial. Contact type dermatitis may be caused by internal application[19]; on the other hand atopic dermatitis may be produced by external contact. The most common examples perhaps are milker's eczema (with positive scratch or intradermal tests to cattle dander) and the atopic form of plant dermatitis. Mitchell and Mitchell[89] report a case of recurrent seasonal dermatitis in which the protein fraction of timothy pollen was the offending cause. This is an instance of atopic dermatitis by contact. These cases are apparently more frequent than recognized. It is important to draw attention to this atopic form of plant dermatitis because the majority of eczemas from grasses and weeds are different and due to contact type sensitivity to the oleoresins of the plants. Herrmann, Sulzberger and Baer[60] report several cases of atopic dermatitis by contact. These authors report penetration of allergens into the human skin by means of new penetrating vehicles. Skin

tests performed with these vehicles produced urticarial reactions of considerable extent appearing within two to five minutes after inunction. The results corresponded closely to those obtained in the same cases with scratch tests. Percutaneous penetration has again been studied by McKee, Sulzberger, Herrmann and Baer.[84] By using vehicles which utilized the combined and reciprocal action of water, propylene glycol, interface active agents, coupling agents and solubizers, staining of the follicles, cutis and epidermis was regular. However, in all instances a color-free band beneath the horny layer and above the prickle cell layer (approximately corresponding to the stratum lucidum) was observed. The authors conclude that this band is a barrier for percutaneous penetration. These results indicate that penetration occurs through the hair follicles into the cutis; there seemed to be an upward movement of the colored material from the cutis into the epidermis.

Infantile Eczema.—Infantile eczema is by no means always a manifestation of atopy. It can rather readily be divided clinically in four groups[35]: (1) Atopic dermatitis, (2) Seborrheic dermatitis, (3) Contact dermatitis (epidermitis), (4) Infectious eczema (chiefly that form called intertrigo).

Plotz [106] reports two cases of eczema of face, neck and arms in infants under one year which were caused by contact with the mother's hair. The hair lacquer used by the mothers was found to be the cause. Jerome Glaser[50] obtained splendid results in two cases of severe infantile eczema with a synthetic milk containing meat particles. These infants had not been relieved by soybean milk. Unfortunately the manufacture of this milk substitute has been discontinued on account of the war. Strickler, Herman and Grumach-Fabian[127], studying forty-one children from nine months to twelve years with eczema (35 atopic, 4 seborrheic, 2 ichthyotic), and nine controls failed to find any deviation of the gastric secretory function in this series.

Many physicians are reluctant to hospitalize patients with infantile eczema. M. A. Green[55] reports a case of a seven-months-old girl whom he had to hospitalize on account of generalized atopic dermatitis. The child developed measles and bronchopneumonia, but eventually recovered. Epstein[35] has investigated hospital mortality and morbidity of infantile eczema. He reports a series of 100 consecutive hospital admissions without a death from 1937 to 1944. Out of these children, twenty-one suffered from twenty-three complications, a morbidity of 23 per cent. A breakdown of the statistics showed that all but one of the complications occurred among the seventy-eight atopic children and only one among the twenty-two nonatopic eczemas. Nearly all complications were respiratory infections or gastro-intestinal disturbances. They are explained as exacerbations of concomitant respiratory or gastro-intestinal allergy. The author concludes that with with the advent of sulfonamides and under proper nursing care, there need not be fear of death in hospitalized infants with eczema. This conclusion should not lead to indiscriminate hospitalization of cases of infantile eczema, but it should eliminate fear in those instances where hospitalization becomes mandatory on account of the severity of the eczema, or for other reasons. The so-called "sudden death from eczema" in infants is also discussed.[35] A hypothesis of toxic effects from phenol-like tar products, in combination with interference with skin respiration and disturbance of the autonomous nervous system, is suggested to explain some instances of this phenomenon. A reminder is given about the toxicity of coal tar and it is suggested that tar preparations should not be used over too great surfaces. Strickler[125] reports five cases of Kaposi's varicelliform eruption. Four of Strickler's cases occurred in infants and children suffering from eczema. They all recovered. His first case, however, followed smallpox vaccination and ended fatally. As we know now that true Kaposi's varicelliform eruption is caused by the virus of herpes simplex, this case belongs to eczema vaccinatum.

Psychosomatic Aspects of Allergic Dermatoses.—The role of psychological factors in dermatoses has long been recognized by some authors. But only in recent years has this aspect received general recognition, under the title of psychosomatic medicine. Evidence for neuropsychiatric disturbances in skin diseases has been presented in the form of studies of groups afflicted with allergic eczemas, by case reports, and by experiments studying the physiological effects of emotions.

Lynch, Hinckley and Cowan[80] present psychobiologic studies of seventeen patients with atopic dermatitis. Thirteen suffered from typical atopic eczema (disseminated neurodermatitis), four presented less extensive eczematous eruptions that were classified as late exudative diathesis of Rost. A definite psychosomatic relationship seemed apparent. The findings would support a concept of dynamic relationship in which constitution, specific allergic sensitizations, personality, and environmental stresses play roles of varying degree in each individual's total reaction and eczema. Physical similarities and tendencies were present in atopy, vigor, rapid pulse rates, good exercise response, lowered basal metabolic rates, and low white blood cell count and all the patients demonstrated suppressed resentment and tension, and all but two had more than average intelligence. Certain other personality factors were commonly present but appeared to be less constant and of less importance. These included appreciable but varying degrees of purposefulness with limited spontaneity; superficial emotional stability and high reactivity; and tendencies to perfectionism, self exaction, and self assertiveness.

Greenhill and Finesinger[57] found that patients with atopic dermatitis show psychoneurotic symptoms more frequently than do the controls. The patients with atopic dermatitis were found to have hostile tendencies, feeling of inadequacy and depressive trends. In these patients was a definite correlation between events which evoked feelings of anger and depression, and exacerbations of the skin eruption. According to Kendall[71] suppressed resentment is the outstanding emotional feature.

A direct effect of psychologic factors is indicated by the following case reports. Wright[143] reports two cases of a psychic etiology in acute dermatitis. Here is the history of one: A man, aged sixty-seven, developed an acute vesicular eruption on the hands and feet within twenty-four hours after his oldest daughter was involved in a serious automobile accident. There was no history of any kind of previous skin eruptions. The daughter recovered and after three weeks of local therapy the eruption disappeared. A year later a younger daughter was seriously injured in an automobile accident and within a few days the eruption reappeared in full bloom. After recovery of the daughter the eruption disappeared and there has been no recurrence since. Epstein[42] reports a case of an eczema of the hands that apparently was caused and maintained by a variety of factors. One evening the patient had a heated argument with a neighbor family about the strained relations of their respective daughters, at the end of which he threw his neighbor out of the house. Within an hour he noticed a papular rash appearing all over his body and shortly afterwards a severe flareup of the eczema of his hands which had nearly disappeared by that time. The role of psychic factors probably is most pronounced and most important in that condition commonly called neurotic excoriations. Although there is no evidence of allergic skin manifestations in most of these cases, they are sometimes mistaken for eczemas and probably concern the allergist as well as the dermatologist. A. Carley[15] presents a psychiatrist's analysis of such a case. The patient was a married woman, forty-nine years of age, who suffered from severe pruritus for four years, and was treated by many physicians apparently without success. Carley analyzes her as a woman, who because of her early rejection by her parents (she was an unwanted sixth child), learned to react to her environment in an aggressive manner. Her parents were emotionally immature and from them she learned

similar inadequate methods of handling her problems. As long as her aggressiveness met with success she remained fairly well adjusted. But when her aggressiveness failed to gain satisfaction (as in bossing her son) she reacted in a more inadequate manner as expressed in her symptoms of severe itching necessitating the personal discomfort of resulting skin lesions along with the undesirable feelings of depression. With the understanding of the situation the patient's symptoms disappeared, but more important, she, her husband and son have spent the most happy six months of their family life.

Mitchell and Curran[88] present an outline of a method of psychotherapy suitable for the allergist. The patient is encouraged to express his feelings freely. Besides the patient is aided to see the fundamental drives and desires behind his emotions. The patient is assured that his talking so freely has been worth while and that he has not been acting foolishly. However, the patient usually does not accept the psychogenic' factors and has his own physical diagnosis of himself. Gradually, however, he becomes encouraged and he begins to talk about his home, family, work, personality needs. Slowly he accepts some of these factors as part of his problem. Some of these patients require the help of a psychiatrist; as a rule—as Kendall[71] states—the search for the focus of suppressed emotion with insight into the frustration circumstance, all are within the ability of the dermatologist or other specialist if he will but take time to listen to the patient.

There are some experimental studies that help to understand the mechanism of psychosomatic relations. Eugene E. Bereston[8] presents an interesting contribution to the influence of the nervous system on skin reactivity. Bereston compared various skin reactions, namely, the histamine flare, the pilomotor reaction to acetylcholin, as well as tuberculin, trichophytin and contact type reactions on patients with hemiplegia and paraplegia. The histamine and cholin reaction was diminished in a high percentage of cases in which nerve degeneration has occurred, that is, in paraplegic individuals. In patients with hemiplegic lesions (located in the brain) in which the peripheral nerves are not degenerated, no such changes were noted. Intradermal reactions to tuberculin and trichophytin showed the same behavior; here too the reaction depends on the degree of integrity of the peripheral nerve axons and the adequacy of the peripheral circulation in paraplegic cases. In experimentally produced contact dermatitis the results were somewhat different; in paraplegic individuals with transverse cord lesions, ten out of the twelve sensitized patients showed stronger reactions on the normal skin; but changes were also noted in hemiplegic patients. In all sensitized cases the skin of the normal knuckle gave a greater reaction to the test dose than did the skin of the affected side. In sharp contrast to these reactions, in experiments with ultraviolet the sunburn-reaction tended to be stronger on the affected skin sides in both hemiplegics and paraplegics. This difference from the histamine reaction appears especially interesting in view of the claim that histamine is responsible for the sunburn reaction.[33] The influence of local anesthesia on experimental contact dermatitis has been studied by Mom and Noussitou.[94] This author found diminished reaction at the site of local anesthesia. Mom and Noussitou[94] performed experiments regarding the influence of the peripheral nervous system on urticarial reactions of the skin. They conclude that the experimental urticarial reaction of the skin is partially controlled by the peripheral nervous system. Blockage of the peripheral nerves by local anesthesia delays and limits appearance and spread of erythema and swelling following intradermal injections of histamine and morphine.

A psychosomatic effect of emotional stress upon the temperature of the skin has been demonstrated by Mittelmann and Wolff[90] during psychotherapeutic (psychoanalytic) interviews. The temperature as recorded in the fingers fell in emotional stress with predominent anxiety, embarassment, humiliation, anger, de-

pression with hostility, guilt and fear of abandonment. In states of emotional detachment—in spite of situations of stress—the finger temperature was high and relatively even. During sexual excitement, there was a rise above the control level. Such an observation of local vascular changes would present some physiological background for the often observed effect of emotions on eczema of the hands. Mom and Noussitou[93] were able to produce positive patch test reactions in persons sensitized to dinitrochlorbenzene by application of saline solution by suggesting that they had applied the chemical. These interesting reports so far have not been confirmed by others. Zeller tried unsuccessfully to repeat Clarkson's[16] experiment who had reported disappearance of a positive intradermal reaction to egg in deep hypnosis. In five experiments, hypnotic suggestion failed to affect the usual response of passively sensitized skin areas, and also failed to affect the skin of patients sensitive to ragweed or to animal dander.

Skin Tests.—There is still quite a controversy about the value of dermal tests (scratch tests and intracutaneous tests) in eczema, especially atopic dermatitis. Sulzberger and Baer[134] present a review of these methods from the standpoint of the dermatologist, with many helpful practical suggestions; their evaluation of these tests appears rather conservative. The reviewer admits readily that the scratch and intradermal tests are far behind the patch test in dermatologic value, but he is convinced that they are of more help in typical as well as atypical manifestations of atopic skin sensitivity than is generally realized by the dermatologist, and of less value than is assumed by many allergists.

Treatment.—Coal tar is still the best topical medication in atopic dermatitis, especially in children. A brief study of its manufacture, composition and use in industrial dermatitis is presented by Frank C. Combes.[18] In view of the fact that coal tars from different sources may vary in their carbon content from 5 to 35 per cent, he recommends Daxalan, a commercially manufactured coal tar paste that contains 3 per cent coal tar (low in napthalene content) 5 per cent zinc oxide and 50 per cent starch in a special hydrophylic base. One should not forget that coal tar is a rather toxic substance, and should not be used on too large surfaces, especially in infants.[35]

Hapamine, the antigenic histamine compound, has aroused great hopes for the treatment of atopic dermatitis. There is quite an argument regarding the efficacy of this drug and the dangers accompanying its use. Rowe's[110] therapeutic trials with hapamine in over 25 patients were uniformly unsuccessful, except for evidence of slight possible benefit in a few cases of atopic dermatitis. His series consisted of various allergic diseases which had not responded to the regular allergic methods. Some authors have reported severe reactions. Braden[12] observed a most severe constitutional reaction following an intradermal test with 0.02 c.c. hapamine. He believes the risk is too great to justify the use of this drug. Rowe[110] states that hapamine is being unwisely recommended, and that the medical profession will again be disappointed and disillusioned as in the case of torantil. Epstein[41] observed in a patient suffering from urticaria very severe whealing reactions from hapamine even in dilutions up to 1:1000. This patient was not abnormally sensitive to histamine and did not react to the refined horse serum, used in the manufacture of hapamine.

There is no doubt that hapamine does not live up to expectations. On the other hand it does not appear to be without merits. There seems to be a general impression that it is of some value in atopic dermatitis and in chronic cases of contact dermatitis. The reviewer has also seen some rather favorable results in a few instances.

Severe untoward reactions can be avoided by not treating hapamine sensitive persons. If a scratch test with horse serum, and a subsequent intradermal test

with diluted hapamine is negative, one should be on safe ground. The need for greater individualization of dosage is now recognized in the manufacturer's directions.

CONTACT DERMATITIS (EPIDERMITIS)
(Eczematous Contact-type Dermatitis, Dermatitis Venenata, "Ekzem" of the European School)

The term "epidermatitis" to designate manifestations of epidermal sensitivity is suggested by Templeton[137] in order to separate it from skin disorders caused by dermal sensitization. This proposal emphasizes the need to replace the ambiguous term of "contact dermatitis"[38], because it conveys the wrong impression that external contact is its characteristic. However, the route of the allergen is immaterial[19], it is the shock organ and other immunologic factors that separate "contact dermatitis" from atopic dermatitis.[38] Epidermitis (contact dermatitis) is mostly but not always based on allergy. Primary irritating substances may produce an identical morphological picture. Neither is there a histopathological difference between the allergic and toxic forms of contact dermatitis. Mom and his co-workers[92] studied the histopathologic changes produced by primary irritation from dinitrochlorbenzene diluted 1:20 and those by an ellergic reaction of a weaker dilution. The lesions produced by the primary irritation are identical with those obtained after sensitization by dinitrochlorbenzene through an allergic mechanism. The picture always consisted of the formation of spongiosis and intraepidermal vesicles invaded by polynuclears and lymphocytes. It was followed by lymphocytic perivascular infiltration of the dermis.

Last year's literature on epidermitis (contact-type dermatitis) consists largely of reports about allergens encountered in military and private life, and industry.

Clothing.—Dolce[28] reports ten cases of shoe leather dermatitis with the typical location on the sides and dorsa of the feet, toes, and ankles. All these patients had an associated hyperhidrosis. Treatment of the hyperhidrosis and a change of the type of shoes proved effective. A case of dermatitis from stocking dye is reported by Hollander.[61] The diagnosis was confirmed by a positive patch test. The sensitization to Tintex dye followed an accidental cut. The role of accidental injury in producing sensitization to chemicals that have been tolerated for a long time previously, should be remembered by all those who take care of cases of industrial dermatitis. Many cases of contact dermatitis from clothing are seen in the army and navy. Carpenter and Banzer[14] report three cases of contact dermatitis from blue uniforms in Navy personnel. Patch tests with their own uniform clothes gave a severe reaction. Dermatitis, wholly or partly due to intolerance by the skin of contact with woolen textiles apparently plays a great role in the British army according to Davies and Barker.[23] During eighteen months they collected 201 cases. They made up a high proportion (16.4 per cent) of the skin patients in one large military hospital, 110 out of 670 admissions. The eruption presents itself in various forms, some cases simply as pruritus or as an urticarial eruption; most cases as various forms of dermatitis. An important manifestation was that of prurigo simulating scabies. The diagnosis was established in most instances either by positive patch tests or by exposure to the khaki material. The prurigo-scabies-like cases gave only faintly positive patch tests and have a tendency to recover with lapse of time. The authors believe this dermatitis chiefly due to intolerance to wool; sensitization may occur spontaneously or as the result of friction by garments, but more commonly its onset is determined by some other dermatosis, mainly, scabies. As the description of Davies and Barker's cases indicates, they belong to different forms of sensitivity, among them, contact, atopic, and mechanical. These authors recommend removal of the irritant

and protection with cotton underwear. Vitamin B and C had no effect in their experience. M. T. Lowance[79] reports three cases of severe dermatitis of the face and neck in children wearing Halloween masks.

Cosmetics.—Howell[64] reports a case of dermatitis of face, neck and ears following "cold permanent waving." Skin test demonstrated that the patient was sensitive to a preliminary lotion, but not to the actual cold waving compound. Howell does not mention of what the preliminary lotion consisted. Keil and Van Dyck[70] found that twenty-five of twenty-six nail polish sensitive patients reacted to patch tests with toluene sulfonamide resin. None of the patients were found sensitive to nail polish remover.

Various chemicals: Forman[44] stresses the fact that contact dermatitis may first or chiefly appear not on the hands that touch the agent, but on those parts of the body that are touched by the hands. He reports a case of acute dermatitis of the left orbit, lobe of left ear and adjoining cheek in a man who was sensitive to self-striking matches. He kept the box in the left-hand trouser pocket and had the habit of holding his face in his left hand while sitting. "Diaper rash" usually means a dermatitis of the diaper region in babies caused by the irritation of decomposing urine. Dobes[27] describes under this title five cases of an acute dermatitis in infants from two to sixteen months of age. The diapers had been passed through an antiseptic rinse. The antiseptic, "Perm-Aseptic" is a primary skin irritant in strong concentrations and a sensitizer in weak solutions. The etiologic relationship was proved by a positive patch test in one of the cases.

Investigation of the causes of contact dermatitis of the hands is often a very difficult problem. Sterling[128] found sensitivity to "Microlene," a germicidal powder used in dishwashing, as cause of a severe, long-standing dermatitis of the hands arms and neck of a waitress. According to Anderson[2a], the true nature of the contact dermatitis of the feet and hands due to rubber is frequently unrecognized. Rubber cement and elastic rubber fabrics are used in the manufacture of shoes, especially of women. The commonest sites involved are the toes and the sides of the heels.

*Drugs**.—Pyle and Rattner[109] report the first case of epidermitis (contact dermatitis) from penicillin. The diagnosis was corroborated by a positive patch test with crystalline penicillin. Binkley and Brockmole[9] report two cases of dermatitis from penicillin in physicians who handled solutions of sodium penicillin. In one case both patch tests and intradermal tests were strongly positive. Face, eyelids and penis apparently are the favorite location of dermatitis in workers handling penicillin. Silvers[123] reports another case. As a patch test with commercial penicillin was positive, whereas a solution of pure crystalline sodium penicillin did not produce a reaction, it was concluded that the dermatitis in this instance was caused by an impurity.

Orland, Flesch and Rothman[99] tested a dentist who developed dermatitis from contact with procaine hydrochloride. He gave also positive tests to butyn, tutocaine, pontocaine, monocaine, larocaine. Many compounds related to procaine were tested; only those reacted that contained an aromatic amino group on the benzene ring and only when the amino group was in the para position. Dore, Prosser and Green[29] report nine cases of morphine dermatitis in a morphine factory. The eruption normally started about the eyelids; the neck was also a common site. The arms and hands were usually affected last. Hollander[62] describes a case of persistent dermatitis of the flexor surfaces of the fingers. It was caused by application of tincture of merthiolate over a period of two years. The eruption was confined

*Eruptions caused by the medical use of drugs are reviewed in the chapter "Drug Eruptions." (See page 317.)

to the distal phalanges. A patch test with tincture of merthiolate was positive. Avoidance of the medication was followed by rapid improvement.

Plants.—Epidermitis (contact dermatitis) from lemon grass oil in eight workers is reported by Mendelsohn.[86] The men had worked on a boat from India which had tanks with lemon grass oil on board. The dermatitis was similar in appearance to poison ivy dermatitis. Since lemon grass oil has many uses, it should be remembered when searching for etiologic agents in contact dermatitis. Lockey[77] reports an outbreak of contact dermatitis, which occurred among men handling varnish containing cashew nut oil, and which was found to be due to faulty treatment of the oil in the manufacturing process. Positive patch tests were obtained with this varnish and with cashew nut oil, but not with properly prepared varnish. Intramuscular injections with cashew nut oil extract accelerated the "hardening" and "desensitization" of sensitive individuals who worked with cashew nut oil. Merrill[87] describes dermatitis caused by various representatives of the Anacardiaceae in tropical countries. These plants cause a distinct and often severe dermatitis corresponding to Rhus dermatitis in the United States. The various species belong in the same family, the Anacardiaceae, and the active principle is the same in all cases. The resinous sap of these plants possesses the dermatitis-producing properties. Various species of the mango tree, producing the familiar mango dermatitis, also belong to this family. The question whether smoke from poison ivy is capable of producing a dermatitis has been investigated again by Howell.[65] His results are interesting both from a theoretical and practical viewpoint. Smoke filtered through cotton did not produce a dermatitis in seven sensitive volunteers. Three additional students acquired a mild dermatitis on the forearms held directly over the flame of the burning ivy. Apparently small particles of leaves, soot and charred matter carried by the smoke were responsible. These experiments indicate that while the actual gaseous smoke or the fumes from burning poison ivy are harmless, people who are burning poison ivy might get a dermatitis from that mixture of gases and particles that is called smoke in common language.

Industrial Dermatitis.—A program for prevention of irritation and sensitization of the skin to chemical compounds is presented by Leon Goldman.[51] There is a great variation in the incidence of occupational dermatitis in plants with different hazards. Schwartz[117] states that there is comparatively little dermatitis occurring in the manufacture of synthetic rubber despite the many irritant chemicals used. Most of the occupational dermatitis occurring in the manufacture of buna S is caused by chemicals added to butadiene and styrene in order to make the reaction possible. Schwartz describes the process of manufacturing and processing synthetic rubber and the numerous chemicals involved. He explains the low incidence of dermatitis in factories making synthetic rubber by the fact that these plants are modernly equipped with mechanical safety devices, and that the safety recommendations are carried out in these factories.

Contact dermatitis from synthetic resins and their manufacture is playing an increasing role as these plastics find a wider field of usefulness. Lockey[78] describes the composition, uses, and the manufacturing processes of the principle synthetic resins (plastics) and presents suggestions for the prevention of dermatitis in workers handling these resins. Anyone who has experience with this type of dermatitis will subscribe to the following recommendations: Persons with an allergic background or suffering from skin diseases should not be employed in the plastic department. Protective clothing with long sleeves should be provided. Facilities should be furnished so that the worker can change from his street clothes to his working clothes. The lockers for street clothes and work clothes should be in separate rooms with a shower bath between them. The dust and fumes in

the work rooms should be removed by intake exhaust fans. Abrasions or skin breaks in workers should be treated immediately as sensitization often starts at the site of such an injury.

Sulzberger[132] mentions the following plastic articles which he has found as cause of epidermitis in recent years: (1) clothing finishes (shorts, stockings, shirts, pajamas, et cetera.), (2) nail lacquers, (3) hair lacquers (pads), (4) lacquers on feathers, hats, et cetera, (5) lacquers on hair pins, (6) wrist watch straps, garter straps, and belts, (7) bottle caps, (8) buttons, (9) artificial jewelry of various kinds, spectacle frames, et cetera, (10) steering wheels, (11) earpieces (of hearing devices, radio receivers, et cetera), (12) false dentures (plates), (13) instruments (physicians', dentists', et cetera), (14) toys and lacquered objects used in games, (15) toilet seat and other paint and furniture lacquers.

Sudden outbreaks of dermatitis in industrial plants frequently present a puzzling problem. Sometimes all one finds is a variety of unrelated dermatoses, and actually there was no special increase, but someone in the plant got conscious of the number of skin cases. However, in many instances, the introduction of new processes or the changes in the composition of chemicals may produce a sudden outbreak. Schwartz[118] reports such an occurrence in a plant manufacturing hydrochloric acid. The change in the process consisted of the addition of soft coal. Schwartz found that a waxy deposit was the cause of the dermatitis. It contained 5 per cent hydrochloric acid. Schwartz and co-workers[120] report allergic contact dermatitis (allergic epidermitis) occurring in a plant that manufactures cemented carbides. Sensitivity to cobalt was found to be the cause of the dermatitis. In a number of cases the eruption was limited to the anti-cubital spaces; in others to the sides of the neck and the eyelids; while in still others the flexor portion of the forearms and backs of the hands were affected. In a few cases the eruption was generalized. The authors recommend thorough elimination of dust and protection from dust for the workers. Some of the workers developed a tolerance. Natural desensitization in workers apparently occurs much more frequently than is generally recognized. Peck, Gant and Schwartz[100] present a report on the subject of "hardening" in industrial allergic dermatitis. Jadassohn in 1923 used the term hardening (Abhärtung) to describe the development of tolerance to sensitizing chemicals in industry. Peck, Gant and Schwartz have observed instances of "hardening" practically in all industries where there are allergic dermatoses. The authors cite a few of these observations in the manufacture of synthetic resins, tetryl, and TNT. Up to 85 per cent of the workers who suffered from allergic dermatitis were able to return to the old contacts without any ill effects. Keil[69] however expressed skepticism that "hardening" actually occurs. The report by Peck and co-workers should stimulate further trials of desensitization in industrial as well as non-occupational contact dermatitis.

Patch tests.—Gaul[49] adds a "past-treatment patch test" to the list of patch test uses. This is a recommendation to test previously used medications in order to find those to which the patient may be allergic and to avoid their further use. There is some argument among dermatologists as to the advisability of such a procedure, partially based on potential dangers of such testing. The reviewer agrees with Gaul's recommendation. By performing patch tests at the appropriate time, and by using only small quantities or weak dilutions in cases of a suspected strong sensitizer, the danger of severe flare-ups or serious side effects can be almost completely eliminated. On the other hand, such testing has been very helpful to the patient in cases where medications other than those suspected were found to be the sensitizer. Last, but not least, the production of a localized dermatitis by the patch test will make the patient more prone to avoid future contact wiith this medication, than a warning based only on a more or less founded suspicion. Sulz-

berger and Baer[134] present a critical review of the uses of the patch test, such as differential diagnosis of eczematous eruptions, patch testing of materials for consumer use, etc., pre-employment patch testing. This article[133,134] is recommended to any one who wants to familiarize himself with the possibilities, applications, limitations and dangers of the patch test. For patients who are sensitive to adhesive tape, Lipman Cohen[76] recommends a zinc gelatin bandage, similar to the familiar Unna boot. This seems a rather complicated procedure. Many patients who are sensitive to ordinary adhesive tape, apparently tolerate Scotch tape. According to Keil[68] the chief value of the patch test with a potent poison ivy extract rests with the fact that a negative test excludes past and present hyper-sensitiveness to poison ivy. A positive test is no proof that the dermatitis under consideration is caused by poison ivy on account of the high incidence of positive reactions in the normal adult population. However, Keil[68] believes the quantitative patch test is an important method of checking the value of treatment in this disease. Keil did not observe untoward effects from his patch test.

Treatment.—Intravenous injections of sodium thiosulfate in contact dermatitis again are recommended by Strickler.[126] He gives 5 injections at intervals from twenty-four to forty-eight hours. The use of thiamin as an adjunct in the control of pruritus is recommended by Pipes[105]; 100 mgms. are given subcutaneously daily for two or three days, followed by an oral maintenance dose of 50 to 75 milligrams, depending upon the course of the dermatitis. Calcium gluconate intravenously in acute cases of poison ivy dermatitis is recommended by Baird[4]; also by Epstein[40] who usually continues after one or two injections with oral medication (chlorocalcium, 2 teaspoons three or four times a day). Goldman[52] considers oral poison ivy therapy as the best specific prophylactic agent, though it gives good but only transitory protection and produces a relatively high percentage of cutaneous reactions. Goldman states that the percentage of reactions may be reduced by careful individualization. O'Leary[98] warns against the therapeutic use of poison ivy extracts. Although some patients tolerate well injections of poison ivy antigen, its use on numerous occasions has been followed by a rapid spreading of the eruption to involve the entire body.

Overtreatment of skin diseases, especially in the acute state, is a frequent source of superimposed dermatitis. In many cases sensitivity to some medication is the cause.

Gaul[49] reports four such cases. However, as O'Leary[98] points out, an exacerbation of an existing dermatitis is not always due to sensitization. An ointment may not be tolerated because it is used during the improper stage, e.g., during the acute phase of a dermatitis.

With the increased and unrestricted use of powerful sensitizers such as the sulfonamides, the incidence of severe, disabling dermatitis from such and similar sources is appalling. There have been further warnings against the indiscriminate topical use of sulfonamides.[1,5,39,104] Abramowitz[1] states that sulfonamide drugs have no place in the treatment of uncomplicated eczematous dermatitis.

MICROBIC ECZEMAS

(Fungous, Bacterial, Parasitic Eczemas)

Epidermophytosis.—The war has brought increased interest in fungus infections of the skin, chiefly due to the epidemics of superficial ringworm of the scalp in children and the frequent occurrence of dermatophytosis of the feet among soldiers and sailors. The allergist is especially interested in the latter. Weidman, Emmons, Hopkins and Lewis[141] present a comprehensive review on the present-day problems of dermatophytosis of the feet. The sometimes difficult problem of differentiating industrial dermatitis on the hands from trichophytids is dealt with by

Peck, Botvinick and Schwartz.[101] These authors found the following criteria practical in differential diagnosis:

1. An active fungus infection must be present before the diagnosis of trichophytid can be considered.
2. The trichophytin test should be positive.
3. If one is dealing with a trichophytid, it should not improve after a suitable removal from contact with industrial irritants.
4. Trichophytids prefer the palms, contact dermatitis the dorsa of the hands.
5. In a case where there is a positive scratch test as well as a positive trichophytin reaction and an active fungus infection, there is the possibility that one may be dealing with a combination of an "id" and an allergic contact dermatitis.

It is more and more recognized that not all cases of "athlete's foot" or of dermatitis of the toes are fungus infections. Hopkins[63] concludes that some of these nonmycotic lesions were due to infection by or sensitization to staphylococcus aureus, or to shoe polish, antiseptics and similar sensitizing substances. Hypostasis and trauma account for other groups of these disturbances of the feet.

The difficulties frequently encountered in establishing the diagnosis of a fungus infection in an eczematoid eruption are not fully appreciated. It is often impossible to demonstrate fungi either microscopically or by culture. Sometimes definite proof can be given only after several months or even years of observation and careful search for a focus. Eventually one may find a new primary blister, especially on the soles, that may yield fungi and clinch the diagnosis. On the other hand, there are many sources of error in the microscopical and cultural diagnosis of fungi. Elastic fibers and other threadlike particles are often mistaken for mycelia by the less experienced examiner. The so-called "mosaic fungi" are easily and frequently mistaken for real fungi. It is practically impossible to prove a diagnosis of epidermophytosis by the finding of spores alone. Cultural methods are also a source of errors. Saprophytes may be mistaken for pathogenic fungi, even by experienced observers. C. W. Emmons[34], principal mycologist of the U. S. Public Health Service, calls attention to the misuse of the name "Trichophyton rosaceum." Of 12 fungi received from various laboratories not one represented this fungus. Ten were strains of fusarium, a saprophyte that has never been demonstrated to cause trichophytosis, one was a basidiomycete and one a strain of trichophyton mentagrophytes. This fungus, the principal source of epidermophytosis of the feet, is better known to the allergist and dermatologist as trichophyton gypsum or its variety, trichophyton interdigitale.

Treatment of epidermophytosis is still very unsatisfactory. That goes both for the plain fungus infections and for the eczematoid forms. While it is usually possible to achieve substantial symptomatic relief, permanent cures are probably rare, except in those hyperacute cases that lead to generalized exfoliative "ids." In these instances apparently the fungi are cast away by the exfoliation, and reinfection is prevented by the high degree of allergy. There is little doubt that many milder cases of epidermophytosis could be cured if more patients would muster enough patience to carry on regular treatment for periods of many months after the clinical signs have subsided. Any new method of treatment of epidermophytosis deserves interest. Keeney and Broyles[67] used sodium propionate in fungus infections of the feet and groins. Sodium propionate is fungistatic for common pathogens. The authors had good results in 55 midshipmen with sodium propionate as a 10 per cent ointment and as powder. However there were some recurrences because some of the men were careless. Contact dermatitis from sodium propionate was observed only once. Soaking of the patients' cotton hose with copper sulfate or copper acetate gave good results in epidermophytosis of the feet in experiments carried out by Crittenden and Joiner.[21] The skin of six patients appeared normal,

11 were improved, 1 became worse. Treatment lasted from one and a half to ten months. Lewis and Morginson[75] recommend ethyl chloride spray for the treatment of trichophytosis. Distinct frosting of the skin is produced. This treatment does not lead to a cure but may be used especially in the vesicular stage because it causes vesicles and pustules to subside and leads to drying of the skin and healing of denuded areas. Weidman and Glass [142] found 10 per cent boric acid in talcum as well as cresatin highly successful in epidermophytosis of the feet. The phenol-camphor treatment of dermatophytosis—a rather controversial subject a few years ago—is again fully endorsed by Phillips.[103] He treated 230 lesions of microscopically confirmed ringworm of the feet, groins and axilla. Phillips' report is rather optimistic. All cases were cured with the phenol-camphor mixture within an average of 4.3 to 4.9 days; the longest took thirteen days. In the control series, Whitefield's ointment with the addition of 0.5 per cent dithronol was used, and with this method, too, all cases were cured within an average of 5.5 to 6.1 days.

The value of trichophyton and oidomycin injections in eczematoid fungus infections of feet and hands is still under discussion. The reviewer has no doubts as to its efficacy in certain cases, but we are far from knowing which cases to select and what dosage to use. Saletta[114] reports very good results in triphophyton dermatitis if the patient is interested enough to continue over a long period of time. Schonwald[116] considers hyposensitization with a mixed trichophytin, the most important feature in the treatment of dermatophytosis. Ayres[3] points to the numerous reports of disabilities from vesicular dermatitis of hands and feet (pompholyx or dyshidrosis) in the armed forces. Heat and sweat may cause severe exacerbations of latent infections. Secondary "id" reactions on the hands, secondary pyodermas, etc., may still further complicate the picture. The cardinal rule in the treatment of such conditions—according to Ayres—is to avoid irritation from overzealous treatment. Very acute cases should be treated first by continuous wet dressings of saturated solution of boric acid or Alibour solution:

℞: Copper sulfate	1.6
Zinc sulfate	5.6
Sat. sol. camphor water ad.	240.00

S. Dilute 2 tablespoons to 1 glass of water, and apply as wet dressings.

Blisters should, in addition, be opened and painted with 2 per cent aqueous solution of gentian violet. Combes[18] recommends the use of coal tar in eczematoid dermatophytosis of the feet and the hands.

Moniliasis.—Intertrigo is a form of microbic eczema of the folds of the skin. Maceration of the tissue is a major contributing factor. The most common causative organisms are streptococcus, staphylococcus, trichophytons, epidermophytons and, last but not least, monilia. The most favored local remedies in intertriginous moniliasis—according to Bechet[7]—are 1 to 2 per cent aqueous solutions of gentian violet, silver nitrate, ammoniated mercury ointment, 40 per cent sulfur paste, 5 per cent chrysarobin. To the reviewer, vioform has proved itself as rather effective in this condition. A 2 per cent suspension of the following composition can be used in most any except the acute cases:

Vioform	0.6
Ichthyol	1.0
Ether	
Alcohol āā ad	30.0

In the later stages 1 to 3 per cent vioform in vaseline is often helpful. Sulzberger[130] states that there are few infections of the skin in which the role of systemic derangements is as apparent as it is in certain cases of so-called moniliasis.

Diabetes, obesity, vitamin deficiencies and other general disturbances can be proved to be determining factors in certain cases. The reviewer agrees fully with this statement. In his experience the most efficient systemic medication in this condition consists of large amounts of vitamin B-complex. Where oral medication is not successful, it should be combined with parenteral therapy with crude liver extract.

Bacterial Eczemas.—Infectious eczematoid dermatitis due to bacterial sensitization, so common and troublesome, continues to be neglected in the literature. It is the opinion of Lane and his co-workers[72] that many of the dermatoses of the hands which are being called dermatomycosis, dermatophytid, contact dermatitis, housewives' eczema, dermatitis due to soap, neurodermite, nummular eczema or bacterid, should be more correctly called infectious eczematoid dermatitis. Systemic administration of sulfonamide drugs and injections of staphylococcus toxoid have been occasionally satisfactory; elimination of a focal infection occasionally proved helpful. In some cases of infectious eczematoid dermatitis, penicillin is of great help. Cohen and Pfaff[17], using penicillin both parenterally and as an ointment, containing 100,000 Oxford units in 30 gms. of ointment base, found this method beneficial in the treatment of infectious eczematoid dermatitis, moniliasis and dermatophytosis with streptococcic pyoderma.

Sulfonamides are widely used in the treatment of bacterial eczemas. Several authors[39,104] warn of the special danger of sensitization in patients suffering from infectious eczematoid dermatitis. According to Pillsbury[104] sensitivity to sulfonamides, especially sulfathiazole, may be easily induced by local application in chronic dermatoses in which there is an element of sensitivity, particularly to pyogenic bacteria. This marked ease of sensitization offers a serious contra-indication to local sultonamide therapy in such cases. Yet the use of these drugs externally as well as internally is sometimes especially helpful in infectious eczematoid dermatitis.[39] To reduce the risks of external sulfonamide therapy, Epstein[39] presents the following six suggestions:

1. Sulfonamide ointments, lotions and powders should be used only with proper indications.
2. Physicians should become aware of the special danger of sensitization in infectious dermatitis.
3. Sulfanilamide should be substituted for sulfathiazole.
4. The patient should be informed that he has become sensitive to a sulfonamide.
5. Penicillin should be used in sulfonamide-sensitive patients.
6. The public should be enlightened about the risks connected with the use of sulfonamides.

Seborrheic Dermatitis.—This condition is also—at least to some extent—an infectious eczema. Experimental data presented by Simon[124] suggests that the human dander allergen is present also in scales of seborrheic dermatitis but absent in numerous other scales and other materials. Frank believes that the allergen is not a constituent of stratified squamous epidermis; nor does he believe that it has its origin in accidental contamination of dander with suspended dust particles from the air. It is possible that the allergen may be of microbic origin. Frank thinks that his findings may be of importance for the study of seborrheic dermatitis. Scott[121] lists among seborrheic eruptions dry and greasy dandruff, follicular seborrheides of the scalp, face, chest and back, axillae, groins and also of the limbs. In Scott's opinion, the seborrheic diathesis is due partly to dietetic indiscretions and partly to a hormonal deficiency. The seborrheic state is a prediabetic state, accompanied by retention of fluids in the tissues. Scott believes that in seborrheic subjects, androgen is in excess in the blood over estrone. The various or-

ganisms found in seborrheic eruptions are *not* the cause. These eruptions can be complicated by superadded coccal or mycotic infections, which are too often thought to constitute the whole of the disease requiring treatment. This consists in dietetic and hygienic measures such as frequent baths, ultraviolet treatment, exposure of the skin to the air, especially cool air. He describes a mixed diet with no excess of fats and carbohydrates. Scott gives Stilbestrol for more severe cases. For the mild hypochromic anemia, found generally in long-standing cases, he prescribed iron and arsenic. As far as local treatment is concerned he warns against unsuitable, ill-timed, irritating local treatments. The first duty is to give the skin a rest. For the purely seborrheic or very little infected eruptions the following ointment is recommended: 2 per cent precipitated sulfur, 4 per cent salicylic acid, 1 per cent resorcin in equal parts of oleum cocois and vaseline alba. In case of coccal infection 2 per cent ammoniated mercury, 6 per cent pix liquida in the same base. These ointments should be applied sparingly and not longer than a few weeks to prevent sensitization. Desensitization by intracutaneous injections of bacterial antigens is definitely useful. While the reviewer does not subscribe to all of Scott's assumptions, his therapeutic approach to seborrheic dermatitis coincides in many instances with that of Scott. Iron is a very helpful adjunct in many cases of seborrheic dermatitis. Sulfur is widely used in seborrheic dermatitis. Downing, Ohmart and Stoklossa[30] recommend a comparatively new suspending agent, methyl cellulose, for improving suspensions of sulfur. Their formula for a smooth, creamy sulfur lotion is as follows: (gm. or c.c.)

Precipitated sulfur	10.0
Spirit of camphor	10.0
Alcohol	80.00
Solution of methyl cellulose, 2%	30.00
Rose water to make	240.00

Other Parasitic Eczemas.—It appears proper to review here eczemas and dermatitis from animal parasites. "Cheese itch," a dermatitis caused by mites, is more common than might be expected by the relatively few reports published. This becomes apparent from a discussion of this subject in the Royal Society of Medicine.[108] Prosser Thomas[138] has probably seen at least 200 cases. The mite is Tyroglyphus longior, and found in the coverings of moldy cheese. Whether the mites produce a toxin has not been settled, but made improbable by Forman's[45] experiments. He found positive patch tests to cheese "dust" in two patients, but had a negative result on his own skin. Dermatitis from grain mites (tyroglyphidae) in two men handling straw packing material is reported by Thomas S. Saunders.[115] The eruption occurred as a papular excoriated dermatitis of the wrists in one instance, and of arms and face in the other. Unlike acarus scabiei, members of the tyroglyphidae family do not burrow into the skin. Saunders believes that such eruptions are more common than is realized. "Grocer's itch" is a dermatitis caused by handling dried fruits. According to Schwartz[119] mites are sometimes found in dried dates, prunes, figs, apples and pears. Animal origin other than scabies may be the cause of pruritic, papular eruptions more often than suspected. Russel C. Anderson[2b] reports a case of such a dermatitis caused by the tropical rat mite, Liponyssus Bacoti Hirst. Mites were found on the patient's body and on the kitchen wall in the vicinity of a cupboard that was infested with rats.

OTHER FORMS OF ECZEMA

Under this heading eczemas of unknown origin will be reviewed as well as those allergic eczemas that do not fit in the other three groups.

Nummular Eczema.—According to P. Gross[58] nummular eczema is a recalcitrant dermatosis consisting of coin-shaped patches of erythematous, vesicular eczema with varying degrees of edema and exudation. The sites of predilection are the backs

of the hands and fingers and the extensor surface of the extremities. The shoulders and the face are occasionally involved. The psychosomatic-minded physician will easily find psychogenic and neurogenic factors. Gross[58] prefers to look for the conditioning factors of Vitamin A deficiency, and such search is rewarded by the finding of biliary tract disease, hypothyroidism or hyperthyroidism.

The value of injections of crude liver extract in treating various forms of eczema, is stressed again by P. Gross.[58] At the present stage of our knowledge the vitamin B complex, as represented by crude liver extract, contains a number of factors which either have not been identified or, like folic acid, have been unavailable for clinical experimentation. One can therefore not expect to duplicate the results obtainable by liver extract injections through the use of single vitamins. Animal experiments by Sullivan and Evans[129] may throw some light on the role of vitamin B avitaminosis in eczemas. These investigators produced generalized cutaneous lesions in rats superimposing vitamin A deficiency on vitamin B complex (other than thiamine) deficiency.

The eruption consisted of numerous small scattered squamous plaques. Microscopic examination showed atrophy of the epidermis and appendages, dilatation of atrophic hair-follicles and excessive hyperkeratinization.

Numerous cases of eczemas are caused by a variety of factors. Templeton[137] reminds us that many times the clinical pictures of epidermal sensitization and dermal sensitization merge when both epidermis and the dermis are sensitized. Templeton discusses several such cases. Probably the most frequently seen examples are from sensitization to drugs. As an example of epidermal and dermal sensitization from plants, Templeton reports urticarial reactions following parenteral or oral administration of poison oak extract in patients suffering from poison oak contact dermatitis (epidermitis). Epidermal and dermal sensitization to foods are relatively rare. A case of ephedrine sensitivity with epidermal sensitivity is presented by Lewis.[74] A contact dermatitis—like bullous dermatitis of hands and feet—followed the intranasal application of ephedrine. A patch test with ephedrine hydrochloride in a dilution of 1:1000 gave a strong blistering reaction with a slight exacerbation of previously affected sites. An intradermal injection of 0.1 c.c. of a 1:1000 solution of ephedrine produced an immediate erythematous urticarial reaction.

Perhaps the most complex eczema is eczema of the hands. This is brought out again by a paper about this condition by Lane, Rockwood, Sawyer and Bland[72], and its discussion by several dermatologists. Out of a series of 475 cases of "eczematoid" dermatoses of the hands, the diagnosis of dermatomycosis, dermatophytid, contact dermatitis or soap dermatitis could be confirmed only in very few of the cases. In a very large number the cause is not known. These authors present the following hypothesis: There are various inciting factors. There may be several complicating factors: excessive soap and water, vasomotor instability, trauma, menstruation, hot or cold weather or focus of infection. There occurs an alteration of host-bacteria relationship. There may be a superficial bacterial invasion of the skin, with or without sensitization. The inciting factor may be removed but the eruption may persist as infectious eczematoid dermatitis, a recurrent superficial invasion of the skin by bacteria of low virulence which relapses when the host-bacteria relationship is disturbed by one or more of the aforementioned complicating factors. Sulzberger[131] suggests among other etiologic factors the possibility of infections with the virus of herpes simplex, especially in relation to nummular eczema.

URTICARIA

Herrmann, Sulzberger and Baer[60] report several cases of contact urticaria. The well-known fact that some children develop an immediate urticarial eruption is

exemplified by two cases where contact with silk and wool respectively produced an immediate urticarial reaction. A scratch test with silk was strongly positive in this case. They emphasize that by no means all silk or wool garments produced these transepidermal reactions. Only certain of the mother's silk clothes produced hives through contact with the skin. They report other instances in bakers and bartenders where swelling and itching of the hands occurred within a few minutes after contact with citrus fruits or wheat, respectively. Gutmann[59] reports two cases of urticaria and angioneurotic edema from Palestine, which were caused by chlorinated drinking water. This etiologic factor seems well established in Gutmann's cases. A case of severe urticaria following immediately the intravenous use of pooled human plasma is reported by Dickstein.[25] By a series of ingenious experiments, Dickstein found that the reaction was due to the fact that the patient was allergic to milk, beef and lamb and that those allergens were present in the pooled plasma. Urticaria caused by sensitivity to mercury used as dental fillings is reported by Marcow.[82] The urticaria started after a visit to the dentist. Removal of each filling was followed by a flare-up; complete relief occurred after all silver fillings had been removed. A contact test with mercury was immediately followed by a local urticarial reaction. Urticaria is thought to be caused in most instances by foods or drugs. Derbes and Engelhardt[24] report two cases which they attribute to inhalants; in one instance to ragweed pollens, in the other to fumes of fresh paint. Urticaria may be caused by still other factors. D'Ingianni[26] discusses the pathogenesis and etiology of urticaria caused by caterpillars. The lesions are produced by the caterpillar hair, the toxin glands or by both. According to Leon Goldman[53] urticaria and dermographism are seen occasionally in patients with scabies, especially in easily excitable and apprehensive persons.

Treatment.—S. N. Saletta[113] reports good results from histamine especially in food urticaria and also in a case of severe dermatographia. Toomey, Kreite and Epstein[139] conclude from their well-controlled clinical experiments that there is no indication that histaminase (torantil) prevents or ameliorates the urticaria of serum sickness. In Eger and Stone's[32] thirty-one cases oral administration of twenty units of histaminase every three hours also failed to shorten the course of the symptoms of serum sickness. Rather encouraging results with the use of hapamine in the treatment of several cases of urticaria are reported by Edrington.[31] Successful treatment of persisting urticaria with synthetic vitamin K is reported by Black.[10] Two milligrams three times daily before meals was adopted as the routine dosage, duration of the treatment varied from one to four weeks. Treatment was carried out only in those cases that did not respond to the usual allergic management. In many instances lesions failed to appear after two days of treatment. The best results were observed in those cases that had a prolonged prothrombin time.

The psychosomatic aspect in urticaria is stressed by Wright.[143] An analysis of twenty-five cases of chronic urticaria revealed that seventeen of them (70 per cent) had some definite shock, worry or nervous exhaustion preceding or accompanying the onset of their illness. Wright reminds us that the allergic threshold may be raised or lowered by emotional tension.

DRUG ERUPTIONS

Drugs are capable of causing a great variety of skin manifestations. Drug eruptions may imitate—so to speak—nearly every other skin disease. To give a few examples, aspirin erythema may resemble perfectly the scarlet fever rash, sulfathiazole may produce erythema nodosum-like eruptions; the bullous lesions from barbiturates at times are indistinguishable from pemphigus. The granulomas of bromoderma resemble malignancies, syphilitic gummas, or fungous granulomas and have been mistaken for them, sometimes with unpleasant consequences for the pa-

tient (Netherton[97]). In recent years the medical profession has become more aware of the high incidence of these drug eruptions, largely due to the numerous, mostly allergic toxicodermas accompanying the use of sulfonamides. The importance of these often severe, and not too infrequently fatal, reactions cannot be overemphasized. For these reasons it seems justified to add to this review a chapter on drug eruptions even if there is some overlapping with the review on drugs by E. A. Brown[13] and the chapters on contact dermatitis and urticaria of this review.

Sulfonamides.—The greatest interest still is commanded by the eruptions from sulfonamides.[66] Under the title "Sensitivity to sulfadiazine resembling acute disseminated lupus erythematosus," Hoffman reports a case of severe sensitivity from sulfadiazine. Another case of fatal bullous dermatitis following the use of sulfadiazine medication is reported by Dardinski[22] under the title "Erythema multiforme bullosum." This case is similar to that previously reported by Greenberg and Messer.[56] Watchfulness for drug sensitivity becomes still more important with the increased use of sulfonamides for chemoprophylaxis. According to Morgan and Turner[95] disasters may follow the therapeutic administration of sulfonamides in persons who had received prophylactic doses when manifestations of sensitivity to the drug were erroneously diagnosed as conditions for which sulfonamide therapy was believed indicated. Among the mistakes listed were scarlatiniform rashes diagnosed as scarlet fever, tonsillar and pharyngeal lesions diagnosed as acute streptococcic infection which were actually manifestations of agranulocytosis. Reactions of extreme severity occurred in patients with sulfonamide agranulocytosis by transfusions from donors who were taking prophylactic doses of sulfadiazine. Morgan and Turner stress that disastrous consequences of sulfonamide therapy can be elminated only when physicians acquire the fixed habit of never prescribing the drugs until it is certain that the condition under treatment does not represent, even in part, a manifestation of sensitivity to sulfonamides. In every instance, fever and skin rash should be first suspected as due to sulfonamides.

There are quite a few reports about sulfonamide eruptions following external application of the drug.[43,66,135,136,102] Of 2,280 patients who were admitted to the dermatologic division of a military hospital during a period of six months, Tate and Klorfajn[135,136] found fifty-five cases of sulfonamide dermatitis produced by local application of the drug. Four of these cases also manifested symptoms of photosensitivity. All the cutaneous lesions were of an eczematous nature. The interval between the start of the sulfonamide application and the onset of the dermatitis in eleven cases was from four to seven days; in ten, from seven to fourteen days; and in nine, more than fourteen days. No noticeable constitutional predisposition to sensitization was observed. Positive patch test reactions were obtained which were stronger after slight scarification of the skin. In some cases, the positive patch test was limited to the dermatitis area. The sensitivity persisted as long as eighteen months in some patients. These authors conclude that the use of sulfa drugs in topical therapy is unwarranted, unless life is endangered or unless the results of healing would otherwise lead to a deformity.

Fisher[43] reviews one hundred cases of sulfonamide dermatitis following local applications. Four of eight patients tested by oral administration of the drug had generalized reactions. Tate and Klorfajn[135] report attempts at oral desensitization in thirty patients suffering from sulfonamide dermatitis. Reactions during desensitization included fever, aggravation of dermatitis, loss of consciousness in one case. In view of the fact that penicillin now is readily available, it seems doubtful whether such a dangerous procedure is still justified. Peterkin[102] reports sixty-five cases of sunlight eruptions due to external application of sulfanilamide. In sixty-one of these cases, sulfanilamide powder was the first sulfonamide drug to be applied. Of 200 other cases that were treated with a 5 per cent sulfathiazole ointment, only one developed a sunlight eruption, although their skin was freely

exposed to light. This observation leads Peterkin to the suggestion that sulfonamide sunlight eruptions are almost invariably preceded by application of sulfonamide powder and that the patient becomes sensitized to the drug by its inhalation. A less hypothetical explanation for the author's observation may be given by the fact that sulfanilamide is a photosensitizer[11,36], but sulfathiazole is not. Allergic light sensitivity may be produced by both, but apparently more rarely by sulfathiazole. An interesting form of drug sensitivity are the so-called fixed drug eruptions. They consist usually of single lesions recurring almost always at the same place. Favorite locations of fixed drug eruptions are the fingers, forearms, and penis. They are frequently characterized by pigmentation. Freeman[46] reports the first case of such an eruption caused by sulfadiazine. The patient showed a slightly raised, bright purplish-red eruption, about the size of a quarter, on the dorsum of the right thumb. He gave a history of having had a similar eruption in the same area about three months previously. The last eruption had followed the second dose of 1 Gm. of sulfadiazine, which was taken for rheumatoid arthritis. Six weeks later, within six hours after having taken 2 Gm. of sulfadiazine, the same eruption recurred. Patch tests with sulfadiazine were negative. Recurrences of the fixed eruption also followed the ingestion of sulfamerazine. The existence of these fixed drug eruptions is not generally recognized. The allergist and practitioner should become more familiar with these lesions. Their recognition has an added importance as sometimes these eruptions turn into generalized drug eruptions if the causing agent is not eliminated.

As a rule, scratch and intradermal tests are negative in drug eruptions. An intradermal test for the recognition of hypersensitivity to sulfonamide drugs is described by Leftwich.[73] Sera from patients receiving sulfonamide therapy from one to fifteen days were used for cutaneous testing for hypersensitivity to these drugs. About 0.05 c.c. of serum was injected intracutaneously on the flexor surface of the arm. The control serum produced an initial wheal of 6 to 7 mm. in diameter, which increased to from 1 to 2 cm. with an erythema up to 20 mm. A positive reaction consisted of an initial wheal similar to that of the control wheal, which increased immediately to from 12 to 18 mm. with pseudopod formation. The accompanying erythema measured 30 to 40 mm. The reaction reached its maximum within fifteen minutes. Delayed reactions were not observed. Tests were made on thirty patients, of whom eighteen were clinically sensitive only to sulfadiazine, and four only to sulfamerizine. A positive cutaneous reaction was reported in twenty-eight (90 per cent). The testing serum was found to be highly specific. Freezing and preservation of the serum in the frozen state for two months did not affect its reaction-producing properties. Heating at 60° C. for three minutes destroyed these properties. Sera obtained from patients receiving the drug for less than five days did not produce a positive reaction. The drug level of the serum did not appear to have any effect on its reaction-producing properties. The cutaneous reaction could be elicited as soon as signs and symptoms of the sensitivity appeared and were obtained in two patients, one and five years after the occurrence of the dermatitis. The author suggests that the sensitizing antigen may be a sulfonamide-plasma-protein combination, the sulfonamide being a hapten.

Penicillin.—Penicillin still holds the record of low toxicity although reports of sensitivity, especially of the skin, are on the increase. As far as I can see, no accidents of very serious nature have been reported as yet. Experimental evidence by Rake, McKee, Hamre and Houck[111] bears out the low toxicity of penicillin. They found that penicillin, even in impure form, is many times less toxic for animals than any other well-known antibiotic substance. The reports of penicillin intolerance indicate that penicillin produces different forms of sensitivity, contact type, as well as urticarial eruptions. Also combinations of different types in the same patient as demonstrated by Morris and Downing's case[96], a bullous dermatitis

from penicillin in a man who had received 1,000,000 units. The dermatitis started with itching and erythema, followed by edema and bullous eruptions. The patient also developed multiple wheals of various sizes. Urticarial reactions to penicillin have been described by Lyons[81] as occurring in twelve, or 5.7 per cent of 209 cases treated in army hospitals. Criep[20] reports a case of severe massive generalized urticaria that developed in a soldier immediately following his second course of penicillin. The urticaria would develop immediately on receiving the injection and was continuous and universal during the time the penicillin was given daily. It disappeared when penicillin was discontinued a week later. In this case, the patient gave a positive intradermal test with a penicillin dilution of 1:100, which did not produce any reaction in four controls. There was further a definite precipitation in blood serum dilutions up to 100. Passive transfer also was positive. The patient did not show any reaction to a test with penicillium extract. Criep believes that penicillin allergy is probably unrelated to sensitivity to penicillium spores. Another case of giant urticaria after intramuscular injections of penicillin is reported by Barker.[6] Scratch and intradermal tests produced an urticarial wheal which persisted for twenty-four hours; tests using autoclaved solutions were negative. The significance of positive whealing reactions from penicillin without proper controls appears doubtful from Welch and Rostenberg's[140] experience. They found that most commercial penicillin sodium is a mild primary irritant when injected intracutaneously, producing within one to two hours erythema and edema. Crystallin penicillin, however, has no primary irritating properties. Contact dermatitis from penicillin eye drops is reported by Selinger.[122] Noteworthy in this case was the absence of any conjunctival irritation in spite of the rather pronounced dermatitis of the lids. Contact dermatitis from penicillin due to professional or industrial exposure has been reviewed in the chapter on contact dermatitis (epidermitis).

Welch and Rostenberg[140] add one more form of penicillin sensitivity to the reports of positive patch and whealing reactions. In a man who had worked with various molds for a period of fifteen years, but who had never received penicillin, they discovered a tuberculin type of reaction both to crystalline penicillin sodium and to several commercial brands. The test person developed an infiltrated erythematous and vesicular lesion that started about six hours after the injection and reached its maximum between 48 and 96 hours. Graves, Carpenter, and Unangst[54] report two cases of vesicular eruptions of the hands and feet respectively which followed injections of penicillin. In the first case the eruption recurred with each succeeding injection and produced also petechiae. The lesions disappeared when penicillin therapy was stopped. An intracutaneous test with penicillin showed a delayed positive reaction in 96 hours. The other patient developed a vesicular eruption of his hands within twenty-four hours after his first injection. He, like the first patient, had had a similar eruption previously. However, in this case the lesions subsided in spite of the continued penicillin therapy. The intracutaneous test with penicillin was negative. Trichophytin test was positive in this case as well as in the first one. The author suggests the following three possibilities: (1) The lesions may have been produced by an antigen common to both penicillin and trichophytin. (2) The bactericidal action of penicillin may have released toxins from these patients' fungus infection. (3) The eruptions may have been due to the penicillin or some impurities. It would seem that the first case was due to a sensitivity to the drug. The second case appears due to toxins liberated from a focus of infection by penicillin. This case demonstrates again that not all eruptions caused by drugs are caused by sensitivity. The fact is well known; one of the best examples perhaps is Milian's "Erythema of the ninth day," following arsenical treatment of early syphilis.

Potter and Whitacre[107] report a case of a severe generalized dermatitis with anemia from barbiturates (luminal plus amytal). It is well worth while to remind us ever

so often of the severe, sometimes fatal, eruptions from barbiturates. Luminal (phenobarbital) is perhaps the most beneficial sedative in all forms of eczemas, but perhaps also the most dangerous in regard to toxic eruptions. Thiouracil, used in the non-surgical therapy of thyrotoxicosis, is an unpredictably toxic drug. Among forty-three patients treated with it by Gargill and Lesses[47], toxic reactions developed in eight, skin manifestations (urticaria, pruritus) in two of these cases. Garrilove and Bert[48] reported dermatitis from thiouracil in two cases. Localized, as well as severe generalized urticaria as manifestation of sensitivity to liver extract, is reported by McSorley and Davidson.[85] Nodular bromodermas are rather uncommon. According to Netherton[97], a painful, nodular, papillomatous pustular lesion, not surrounded by acute cellulitis, should make us consider bromoderma. The most striking feature of this type is the high incidence of severe pain and tenderness of the lesions. Netherton reports four cases. The diagnosis is important because this condition may be mistaken for a fungus infection, syphilis or even a malignancy. Recognition of papillomatous bromoderma will prevent surgical interference to which these lesions are at times subjected.

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✶ *In Memoriam* ✶

EDWIN J. BARNETT

Dr. Edwin J. Barnett of Spokane, Washington, an Active Fellow of the American College of Allergists, died suddenly as the result of coronary thrombosis, March 29, 1945, at his home.

He was born March 30, 1894, at Peoria, Illinois. He attended the medical school of the University of Illinois, from which he received his M.D. degree in 1916. Doctor Barnett later took postgraduate work in pediatrics at Harvard University Medical School. During the first world war he was in France, attached to the hospital unit of Spokane doctors and was invited by the late Dr. Peter McCornack to come to Spokane as his associate.

Doctor Barnett was a member of the American Academy of Pediatrics, the American Medical Association, Washington State Medical Society, Spokane County Medical Society, North Pacific Pediatric Society, Nu Sigma Nu Medical Fraternity and a diplomate of the American Board of Pediatrics. He specialized exclusively in pediatrics with special work being devoted to allergy. He was the discoverer of tick paralysis, concerning which he presented a paper at a recent meeting of the American Medical Association at Atlantic City, New Jersey.

At the request of a group of business associates and close friends of Doctor Barnett, the Spokane County Medical Society has been asked to supervise the formation of a memorial fund to honor him and to be used in establishing a suitable memorial to him at one of the hospitals.

Doctor Barnett is survived by his wife, a daughter and a son.

The College has lost a valuable member in the passing of Dr. Edwin J. Barnett.

FRED W. WITTICH

MORTON GUZY

Dr. Morton Guzy, an Active Fellow of the College, died July 20, 1944, at Bridgeton, New Jersey, where he had practiced medicine since 1941. Death was caused by a heart ailment. He was born in New York City, February 17, 1915.

He was graduated from the Medical College of Virginia in 1939 and served his interneship at Philadelphia Jewish Hospital. Doctor Guzy was a member of the staffs of Philadelphia Jewish Hospital, St. Luke's Children's and Medical Center and the Bridgeton Hospital. He was a member of the American Medical Association, New Jersey State Medical Society and Cumberland County Medical Society. He was also a courtesy member of the Philadelphia County Medical Society and Alumni Society Medical College of Virginia. Doctor Guzy was affiliated with Phi Beta Kappa and Chi Beta Phi fraternal organizations.

His interest in allergy included all types of the specialty, particularly the pollen variety, and he had engaged in special work in allergy with Dr. Erich Urbach at the Philadelphia Jewish Hospital.

Doctor Guzy was an enthusiastic member of the College. His untimely death is a loss to our organization.

FRED W. WITTICH

Questions and Answers

What is known about cocoa butter sensitivity?

M.D., Pennsylvania.

Cocoa butter has been listed as causing irritation in persons working in cocoa butter factories. It has been used extensively in pomades, salves, cold creams, vanishing creams and fine soaps, and is a base for ointments and for suppositories. Sensitivity is described in the book by Prosser R. White, "The Dermatoses or Occupational Infections of the Skin," 4th edition (London), H. K. Lewis and Company, 1934, page 273. This knowledge would indicate that the patient requires patch testing with the material at fault, although it should be understood that the medication which the cocoa butter carries is more often the cause of dermatitis than is the vehicle itself.

What procedures are used to distinguish between chronic dyspnea of allergic origin and cardiac failure where the clinical features are vague?

M.D., Minnesota.

In general, the differentiation between the dyspnea of bronchial asthma and that due to cardiac disease is not difficult. In two groups of cases, however, the distinction may be at once difficult and highly important from the standpoint of therapy.

The first of these, paroxysmal nocturnal dyspnea due to acute left ventricular failure, may simulate exactly the paroxysm of bronchial asthma. It may be brief, unaccompanied by bloody sputum, and may come without the warning of previous exertional dyspnea. However, there are three important differences: (1) There is usually evidence of an increased load upon the left ventricle, either hypertension or an aortic valvular defect; (2) There is clinical and/or x-ray evidence of left ventricular enlargement and/or electrocardiographic evidence of myocardial damage; and (3) The arm-to-tongue circulation time is practically always prolonged, often two or three times normal. This latter value, measured by any one of a number of methods (the saccharin method of Fishberg, Hitzig, and King[1] is quite satisfactory) is an extremely valuable diagnostic aid. It is always normal in *uncomplicated* bronchial asthma.

The second group of cases presents a more complicated problem. These are the patients with bronchial asthma of long duration with obstructive emphysema of greater or less degree who begin to exhibit exertional dyspnea, cyanosis, engorgement of the systemic veins, and possibly edema. Ordinarily these symptoms mean heart failure, and since it is well known that emphysema results in right ventricular strain and occasionally frank heart failure, it is only natural that the appearance of these symptoms in an asthmatic should be looked upon as evidence of cardiac weakness. This in turn inevitably brings about a cardiac regime which adds further complications in the life of the unhappy asthmatic without producing any substantial benefits.

It is important to realize that *all* the above symptoms may be present in the emphysematous asthmatic *without* demonstrable evidence of heart weakness and due solely to pulmonary causes (loss of lung elasticity, decreased vital capacity, increased residual air anoxemia, dilatation of cervical veins due to repeated paroxysms of asthma, increased intrapleural pressure, and compression of the inferior vena cava due to pressure from a low diaphragm).[2]

Since heart failure does occur as a result of emphysema and is manifested only by an *increase* in the dyspnea, cyanosis, venous engorgement, and edema, how can one determine when the cardiac element begins to predominate?

X-ray evidence of right ventricular enlargement is convincing but may be borderline for long periods. Much more valuable is the determination of the venous pressure. Like circulation time determinations, it is a simple procedure; and when performed with reasonable care as to details[3], will afford an excellent measurement of right heart efficiency. It is normal or only slightly elevated in emphysema uncomplicated by heart failure[4] and considerably elevated in right heart failure.

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What are some of the failures in the treatment of hay fever attributed to, and how are they to be avoided?

M.D., Missouri

The treatment of hay fever consists of other important factors besides hyposensitization. Failures are, as in any scientific procedure, frequently the result of untested assumptions, inadequate control measures, careless care of extracts and apparatus, and faulty conclusions not based on facts.

It is better to treat a few patients adequately, rather than treat a large "assembly line" inadequately. Among the ways of going astray are:

1. Failure to individualize the patient. There is a tendency of the less experienced to apply the same dosage schedule regardless of the physicial condition of the patient or to attempt to adopt a particular method of specific desensitization.

2. Injudicious selection of the three general methods of hyposensitization treatment, and failure to base the dosage on the susceptibility of the patient. In some instances, two or more methods may be used in the same patient. Some patients obtain very satisfactory results on preseasonal treatment alone each year. Another group having received preseasonal therapy in the properly prescribed manner and having reached the top doses just prior to the season will not receive adequate relief. Treatment should be continued coseasonally on a "primary" coseasonal schedule just as though the patient had not received preseasonal therapy. This is given in 10 or 20 pollen units (0.1 c.c. of 1:5,000 dilution, equals 20 units). The correct initial dose is the smallest amount which gives relief. If 20 units relieve symptoms, the same dose is given daily. Adequate dosage gives 75 per cent relief for one to two days. It is rarely necessary to give more than 80 units (0.4 c.c. of 1:5,000) and the interval lengthened to three days. If a patient has symptoms at the time of injections, 0.3 c.c. of epinephrine 1:1,000, or a mixture of equal parts of epinephrine 1:1,000 and three per cent aqueous ephedrine administered with the pollen gives relief. Some patients after receiving treatment by these two methods may still have symptoms. Then, irrational as it may appear, daily injections of 1:5,000 as well as concomitant biweekly injections of 1:50 may be indicated in doses of one-half or less of the preseasonal top dose. The biweekly injections serve as a maintenance dose to prevent loss of what tolerance the patient has received while the small daily injections are given for present relief of symptoms.

Some patients are fortunate to receive adequate relief with six to twelve injections during the season, by following the primary coseasonal schedule. When a patient reports two or three weeks before the season, it is best to advise primary

coseasonal treatment or give a few preseasonal doses with no attempt to reach the proper top dose, and then follow with coseasonal treatment.

When a patient is away from home during the summer, coseasonal or perennial treatment may be tried. The latter method reduces the number of injections during the summer vacation. When relieved coseasonally and continuation with perennial treatment is desired, weekly injections are given following the season according to the preseasonal method, and when a maintenance dose is reached, the latter is repeated twice monthly throughout the year until about one month before the next season. The dose is then rapidly raised to the top dose with weekly injections.

3. Failure to consider family or genus specificity. Much accumulated evidence would indicate that although pollens which are biologically related show common antigenic properties, they are not completely identical for all pollens or for other members of the same family. When making a clinical application of this information, it is better to test with several different species among the pollen families, tribes, or genera. The best therapeutic results are obtained by including in the treatment extracts all of those species in proper proportion to which the individual is *actually exposed* during the period of his symptoms.

When dealing with unrelated pollens, such as ragweed and English plantain, or ragweed and the grasses, or trees and grasses, the top dose should be independent for all unrelated pollens and not represent a composite. The top dose required for grasses is usually less than that for weeds. Combined treatment with grasses and weeds are frequently very satisfactory.

4. The failure to recognize the importance of food and other inhalant allergens in pollenosis.

The symptoms of, at least, three-fourths of the patients clinically sensitive to pollens are also due to one or more foods or inhalants or both, which require avoidance measures for adequate treatment of the pollenosis. These offending foods may frequently be eaten out of season without causing symptoms. In some cases of pollenosis they are made comfortable without other measures than food restrictions and avoidance of other inhalant offenders. This has been found particularly true of seasonal asthma complicating pollenosis. All patients with seasonal hay fever should be routinely tested with the foods eaten most frequently as well as those foods not likely to be eaten except during the hay fever season, such as watermelon, cantaloupe, certain fruits, et cetera.

The intensity of the allergic stimulus would appear more important than the kind of stimulus, so concomitant, infective, contact, or physical allergy must be considered as influencing the symptoms.

5. Failure, as the result of placing entire dependence on direct skin tests, to determine the clinical pollen excitants when making an extract for hyposensitization. Positive skin reactions frequently occur with pollen which do not cause symptoms in the patient. A pollen giving a positive mucous membrane reaction is more often the cause of the patient's symptoms. When there is multiple sensitivity to pollens or a pollen occasionally gives a negative skin reaction which is strongly suspected as a clinical offender because it is toxic, and coincides with symptoms and atmospheric prevalence, the opthalmic and nasal contact tests may respond. Passive transfer is considered most reliable with pollens and should be used where there are unsuitable skins (dermographia, et cetera).

6. Most constitutional reactions are due to carelessness. They may be produced by:

Rapid forced injections deep into the muscle; failure to determine if the needle is in a blood vessel; failure to dilute concentrated solutions adequately or not including epinephrine when top doses are reached; failure to reduce the dose when a new or fresh lot of extract is substituted; failure to test the patient intradermally with low serial dilutions before determining the initial subcutaneous dose;

failure to caution the patient to not indulge in violent exercise immediately following the injection; failure to ask the patient if the last previous injection caused itching or a local reaction larger than a half dollar, or whether there was some nasal stuffiness or sneezing following the previous treatment; failure to reduce the dose if more than three weeks have elapsed since the previous dose; failure to impress the patient with the importance of receiving the injections regularly on schedule.

Effect of Ergotamine Tartrate and Neosynephrin hydrochloride on the Work Capacity of Human Muscle. Kotalik, G. C., Maison, G. L., and Pfeiffer, Carl: Am. J. M. Sc., 206:503, 1943.

In an effort to determine whether the asthenia after the use of ergotamine tartrate was due to the drug or whether it was coextent migraine phenomena that the drug was unable to eliminate, the authors used twelve subjects and the Maison ergograph to the point of fatigue to measure work capacity. No significant decrease in work output occurred after the intramuscular injection of ergotamine tartrate (¼ to ¾ mg. dosage). There were few subjective symptoms. The work capacity was also tested after injection of 4 to 10 mg. neosynephrin hydrochloride. Work capacity increased after this. Muscle weakness, therefore, was not due to direct action of ergotamine tartrate. The author postulates that some predisposing factor of migraine must potentiate the slight effect of ergotamine tartrate on striated muscle. The work capacity was slightly increased by a placebo injection.

Systemic Allergic Reaction Induced by Yellow Fever Vaccine. Swartz, Harry: Jour. Lab. & Clin. Med., 28:1663, 1943.

Case report of anaphylactic type response in egg-chicken-sensitive patient to a single immunization injection of yellow fever vaccine. Vaccine proven to be instigating agent by P-K testing. Evidence offered to substantiate statement that reagenic fraction of yellow fever vaccine is related to both egg white and chicken meat, but resembling former more closely. Egg and chicken sensitivity by history or skin test is an indication to give yellow fever vaccine carefully.

Atmospheric Pollen Surveys in Brazil

(Continued from Page 286)

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News Items

ANNUAL MEETING OF BOARD OF REGENTS

At the annual meeting of the Board of Regents of the American College of Allergists, held at Cleveland, June 2 and 3, the following Associate Fellows were elevated to Active Fellowship in the organization:

Dr. Leon Bentolela, Buenos Aires, Argentina
Dr. James T. Burns, Washington, D. C.
Dr. C. H. Glover, Memphis, Tennessee
Dr. Edley Jones, Vicksburg, Mississippi
Dr. Stephen T. Manong, Niagara Falls, New York
Dr. Benjamin Zolov, Portland, Maine

Membership in the College, reported at this meeting, was: Active Fellows, 390; Associate Fellows, 55; Honorary Fellows, 15; Corresponding Fellows, 3; Total, 463.

Those nominated to the various offices in the College, whose names were listed on the mail ballot sent to all Active Fellows, received a majority vote. Their terms of office extend from July 1, 1945, to July 1, 1946. The officers elected are:

President, Dr. Harry L. Rogers, Philadelphia, Pennsylvania
President-Elect, Dr. Leon Unger, Chicago, Illinois
First Vice President, Dr. Hal M. Davison, Atlanta, Georgia
Second Vice President, Dr. Michael Zeller, Chicago, Illinois
Secretary-Treasurer, Dr. Fred W. Wittich, Minneapolis, Minnesota

The Regents elected to three-year terms, extending from July 1, 1945, to July 1, 1948, are:

Dr. Hal M. Davison, Atlanta, Georgia
Dr. Merle W. Moore, Portland, Oregon
Dr. Homer E. Prince, Houston, Texas
Dr. George E. Rockwell, Milford, Ohio

The Regents serving on the Board July 1, 1945 to July 1, 1946, are:

Dr. Ethan Allan Brown, Boston, Massachusetts (1946)
Dr. Hal M. Davison, Atlanta, Georgia (1948)
Dr. Merle W. Moore, Portland, Oregon (1948)
Dr. Homer E. Prince, Houston, Texas (1948)
Dr. George E. Rockwell, Milford, Ohio (1948)
Dr. Harry L. Rogers, Philadelphia, Pennsylvania (1947)
Dr. J. Warrick Thomas, Richmond, Virginia (1946)
Dr. Leon Unger, Chicago, Illinois (1947)
Dr. Orval R. Withers, Kansas City, Missouri (1946)
Dr. Fred W. Wittich, Minneapolis, Minnesota (1946)

It was voted to conduct an intensive instructional course in allergy next November 5 to 10, inclusive, at Northwestern University, Chicago, Illinois, with clinical facilities at Wesley Memorial Hospital. The schedule of subjects was arranged, and the speakers named.

The "Committee on Graduate and Undergraduate Education in Allergy" will be known as the "Educational Committee" of the College.

Dr. Louis S. Robins, Chicago, an Active Fellow in the College, was elected to the Editorial Staff of the ANNALS OF ALLERGY.

NEWS ITEMS

It was decided that the Progress in Allergy notes and Annual Reviews of the Literature, appearing in the ANNALS, be bound each year.

The Spanish supplement, which is published under the auspices of the College and which contains abstracts in Spanish of the scientific articles appearing in the ANNALS, will carry Spanish advertising and will also be enlarged to include Spanish translations of the Progress in Allergy notes and the Reviews of the Literature.

It was voted to publish a roster of College Fellows in January, 1946.

Dr. George R. Rockwell, Chairman of the Standardization Committee, reported on the progress which this Committee has made so far. Editorials will appear in future issues of the ANNALS concerning the plans for the work to be done and the accomplishments attained by this Committee.

The subject of certification of allergists was discussed, and it was decided that this matter be tabled until the next annual meeting of the Board of Regents.

It was planned to hold the next annual meeting of the College in 1946, just prior to that of the American Medical Association, in the same manner as the 1944 meeting of the College was conducted.

It was voted to establish an Honor Section of the College. This will be known as an Advisory Council to the Board of Regents. Membership in this Section will signify the highest distinction a Fellow can attain in the College. Eligibility to membership in the Honor Section will require 20 points which will be apportioned as follows: Officers will receive one point for each year in office; instructors, two points for each course presented; papers published in the ANNALS will be rated according to their content and length.

The functions of the New and Unused Therapeutics Committee, of which Dr. Ethan Allan Brown is Chairman and of which Drs. L. O. Dutton, Philip M. Gottlieb, George E. Rockwell, Frank A. Simon and Erich Urbach are members, will be initiated. It was decided that a page headed "New and Unused Drugs" be included in the ANNALS in which articles will be published which will be signed by the member of the Committee making the report or by the Chairman of the Committee. The literature concerning important drugs will be reviewed and given a trial, when feasible. Members will be asked to submit questions concerning drugs. Certain preparations about which there has been controversy will be investigated first.

The Questions and Answers department of the ANNALS will be revived. Members are urged to submit questions which will be referred to the best known authorities for reply.

THE INTERNATIONAL ASSOCIATION OF ALLERGISTS

After careful planning and study by representative officers of the most important existing national allergy societies, it has been mutually agreed to organize an International Association of Allergists. The time is considered opportune, with the cessation of global conflict and the accelerated universal interest of medical men in applying allergy to their various specialties, for an association which would encourage and promote international assemblies for the purpose of disseminating information relating to allergy throughout the world. Pan American and Pan European Sections will be affiliations of the Association.

Plans are in progress for holding the first International Congress in Paris in 1948 when universal standards of terminology and classification of allergies will be adopted.

Preliminary to this program, it is proposed that the same subjects will be the theme of the first Pan American Congress to be held under the auspices of the College at its next annual meeting.

The College is very fortunate in having some of its officers invited to participate in the organization of this association by the officers of the outstanding al-

lergy societies of other nations. The Board of Regents has officially accepted the proposals offered by the International Association. Standards for eligibility to membership and all other important functions are now being formulated and incorporated into the By-Laws.

MEMBERSHIP

At the June meeting of the Board of Regents of the College, the following members were elevated to Active Fellowship in the organization:

Dr. C. H. Glover, Memphis, Tennessee
Dr. Edley H. Jones, Vicksburg, Mississippi
Dr. Stephen T. Manong, Niagara Falls, New York
Dr. Benjamin Zolov, Portland, Maine
Dr. Leon Bentolila, Buenos Aires, Argentina

Those elected to Active Fellowship during June and July, 1945, are:

Dr. William Roland Crowe, Atlanta, Georgia
Dr. Royal H. Finney, Pueblo, Colorado
Captan Kenneth J. Weiler, Tampa, Florida

Associate Fellows elected to membership during June and July, 1945, are:

Major Irwin Alters, Overseas
Dr. William H. Blank, Birmingham, Alabama
Lt. B. B. Burrill, Bainbridge, Maryland
Dr. Robert E. Jameson, Davenport, Iowa
Dr. Howard J. Lee, Hamilton, Ontario, Canada
Captain Benjamin Lieberman, Oakland, California
Dr. Emanuel C. Liss, South Bend, Indiana
Dr. Frank C. MacCardell, Providence, Rhode Island
Dr. Lewis B. McCullough, Mansfield, Ohio
Dr. Morris Scherago, Lexington, Kentucky

NEWS ITEMS

The Board of Regents is pleased to announce the election to Honorary Fellowship in the College of Dr. Jiminez-Dias of Madrid, Spain, Dr. Pasteur Vallery-Radot of Paris, France, and Dr. Abelardo Saenz of Montevideo, Uruguay, for their outstanding and meritorious contributions in the field of allergy. The College's efforts to foster and encourage a friendly international co-operation of specialists interested in allergy has been rewarded by the tentative mutual plans already made for the holding of a Pan American Congress of Allergy under the auspices of the College at its next annual meeting to be held next June with the American Medical Association.

Dr. Edward A. Dickson, an Active Fellow of the College, has announced the opening of his office for the diagnosis and treatment of allergy at 19 Garfield Place, Doctors Building, Cincinnati 2, Ohio.

WANTED: RESIDENTS OR FELLOWS IN ALLERGY.—Facilities for clinical study and research available. Periods of training from 6 months to 2 years with compensation. Vaughan Memorial Clinic, 201 West Franklin Street, Richmond 20, Virginia.